

Glossary

Atom

Atoms are the basic building blocks that make up matter. Each atom belongs to a particular chemical element. There are 92 naturally occurring elements and at least 24 artificially produced elements, all of which are methodically listed in the periodic table. The atoms making up the various elements differ in their structure (see atomic model).

Atomic model

There are various models that show how an atom is structured. However, they are all based around the assumption that an atom comprises a nucleus, which is made up of a varying number of positively charged protons and neutral neutrons depending on the element, as well as negatively charged electrons, which rotate around the nucleus. The nucleus of the atom is what matters when it comes to nuclear magnetic resonance methods.

Molecule

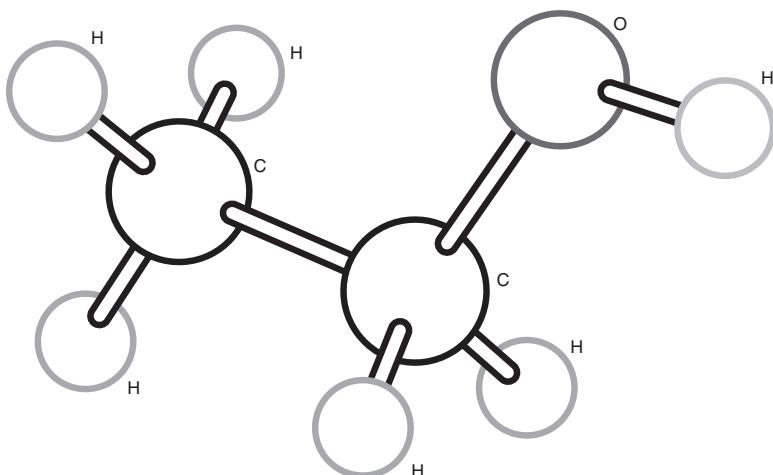
When several atoms are held together by chemical bonds, we have a molecule. An ethanol (alcohol) molecule, for example, comprises two carbon, six hydrogen and one oxygen atom (see Fig. 1). The type of bonds between the atoms and their spatial arrangement in the molecule is referred to by chemists as the structure of the molecule. It determines the chemical environment of the individual atoms

within the molecule, which, for example, is different for a hydrogen atom bonded to an oxygen atom than it is for one bonded to a carbon atom.

Molecule

A molecule consists of atoms of different elements connected by chemical bonds.

Example:
Model of the ethanol molecule



Ethanol consists of
1 oxygen atom (O, dark gray)
2 carbon atoms (C, black)
6 hydrogen atoms (H, light gray)

Structural formula: $\text{CH}_3\text{-CH}_2\text{-OH}$

Figure 1 Example of a simple molecule: Ethanol (alcohol).

Nuclear spin

Nuclear spin refers to the angular momentum generated by the rotation of the atomic nuclei; the nuclei therefore “spin” around themselves. All atoms have nuclear spin with the exception of those with an even number of protons *and* an even number of neutrons. The nuclei of hydrogen atoms (H), which consist of only one proton, are especially important when it comes to nuclear magnetic resonance.

Magnetic moment

If a nucleus has nuclear spin, the rotation of its electrical charge results in a magnetic moment. Such a nucleus then behaves like a small magnet with two opposing magnetic poles, which are influenced by magnetic fields and electromagnetic waves.

Frequency

Frequency refers to the number of occurrences per unit of time that a wave oscillates or a gyroscopic movement occurs, i.e. how quickly a recurring wave or gyroscopic movement passes through the same point. The base unit for measuring frequency is hertz, where 1 hertz corresponds to one oscillation or repetition per second.

Precession

If an external magnetic field is applied, the magnetic moment of the nucleus (comparable to a compass needle) aligns itself with respect to the axis of the magnetic field and rotates around the latter. This gyroscopic movement is known as precession motion. The precession speed of the magnetic nuclei has a certain frequency, the so-called Larmor frequency. It depends on the strength of the magnetic field applied, the properties of the nucleus and the chemical environment of the nucleus. For protons, the Larmor frequency for a magnetic field strength of 1.5 tesla is exactly 63.9 megahertz. By contrast, in the earth's magnetic field (approx. 30 microteslas at the equator and 60 microteslas at the poles) the Larmor frequency of a proton is between 1 and 2.5 kilohertz. By way of comparison, VHF radio signals are around 100 megahertz.

Radio waves

Radio waves are electromagnetic waves. They can be created by using an alternating current and have a certain wavelength and frequency (and therefore energy). With NMR methods, radio waves are directed onto the sample, either continually or in short pulses, and interact with the nuclear spin.

Excitation

When radio waves of the correct frequency are applied to a chemical substance, the magnetic nuclear spins absorb their energy, i.e. they become “excited”.

Resonance frequency

During excitation, the rotating magnetic nuclear spins only absorb radio waves of a certain frequency; this is known as the resonance frequency. It corresponds exactly to the Larmor frequency (see precession) and as is the case with the Larmor frequency, it depends on the external magnetic field, the chemical environment and the properties of the nucleus measured. As per the rules of quantum chemistry, the nuclear spins reach a higher energy level when they absorb radiation at the resonance frequency.

NMR

Nuclear magnetic resonance (NMR) refers to the reaction of magnetic nuclear spins after being exposed to high-frequency radio waves. In chemical analysis, NMR is one of the best methods to examine the structure of molecules. The nuclei of hydrogen atoms (H) are especially important when it comes to nuclear magnetic resonance. However, NMR experiments can also be used to examine the nuclei of other suitable elements with nuclear spin.

NMR spectrometer

Device used to measure an NMR spectrum. The key component in an NMR spectrometer is the magnet together with the probe head as well as a radio wave transmitter and receiver, which is set to the resonance frequency range of the nucleus to be examined. There are also various auxiliary electronic devices up- and downstream from this, including the pre-amplifier, amplifier and modulators. A computer is used to control the experiment and then to analyze the results.

NMR experiment

The main magnet in an NMR spectrometer ensure that a strong and stable magnetic field is applied. The chemical substance to be analyzed is placed into the probe head in a special test tube between the pole shoes of the magnet. The strong magnetic field means that the nuclear spins of the hydrogen atoms in the molecule are aligned close to parallel (or antiparallel) to the magnetic field and precess around the axis of the magnetic field at their Larmor frequency (see Fig. 2). Then radio waves are sent to the sample via a transmitter. If the radio waves reach the resonance frequency of the nuclear spins, these are excited. After the radio waves are turned off, the excited nuclear spins return to their original state and re-release the energy they have absorbed, in the form of radio waves of the same frequency. Here, the nuclear spins induce an electrical signal in the receiver coil, which is then recorded. This makes it possible to measure an electromagnetic wave over a certain period of time; this is referred to as a time-dependent electromagnetic wave function. The wave function has a frequency, which corresponds exactly to the resonance frequency of the nucleus measured.

NMR spectrum

The NMR spectrum (also referred to as a “frequency spectrum”, see Fig. 4) is a graphical representation of the various resonance frequencies of the nuclear spin measured in a molecule.

Chemical shift

In NMR experiments, the local magnetic field at the site of a hydrogen nucleus is influenced by the electromagnetic properties of the neighboring atoms in the molecule, in particular by those of the chemically bonded neighboring atoms. This chemical environment of the nuclear spin therefore changes the resonance frequency of the bare nucleus. In other words, from an NMR perspective there are various types of nuclear spins in a molecule depending on how these are bonded in the molecule. This results in the measured frequencies being shifted up or down by tiny amounts depending on

the electrochemical properties of the neighboring atom. This effect is referred to as "chemical shift". It makes it possible to differentiate between and attribute the differently bonded hydrogen atoms within a molecule based on their resonance frequencies, and means that the structure of the entire molecule can be examined.

The NMR experiment

How the nuclear magnetic resonance method works

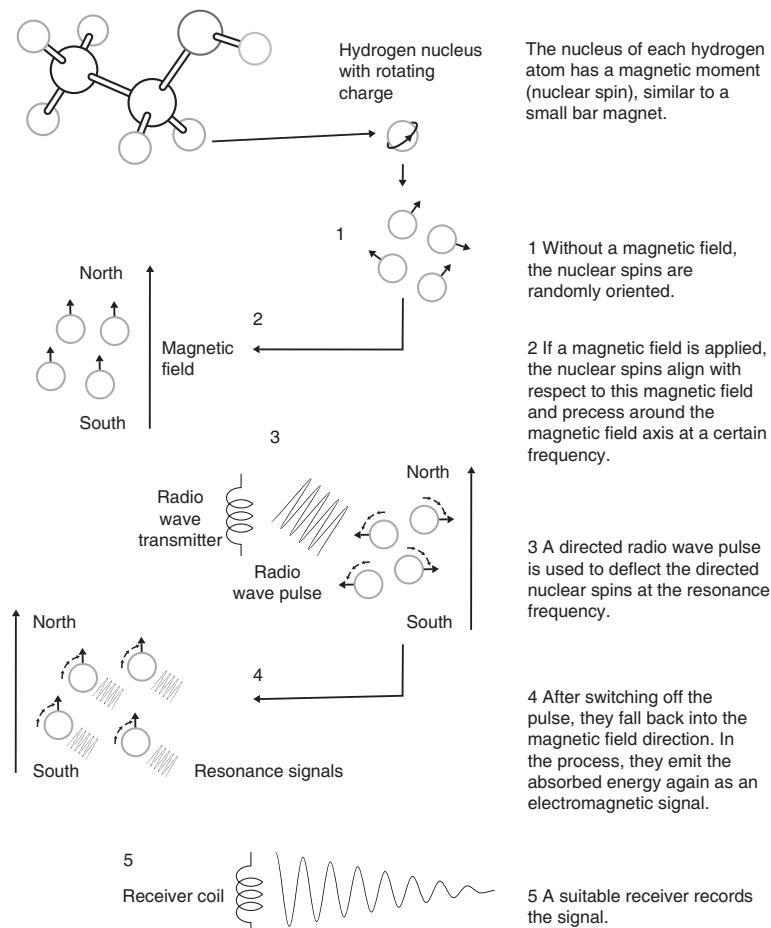


Figure 2 Structure of an NMR experiment.

Fourier transform

The Fourier transform (FT) is a mathematical operation, which determines the frequency of the time-dependent electromagnetic wave function. As the measured NMR signal is usually produced as a result of a variety of superimposed waves with different resonance frequencies, which can originate from the various different types of hydrogen nuclei within a molecule, these can be filtered out using the FT and represented in a frequency spectrum (see Fig. 3). However, the conversion process used in NMR is so complicated that it can only be carried out using powerful computers. The major benefit of the FT can be described by using an analogy: Imagine that you had to solve a complicated arithmetical problem in your head using roman numerals – a long-winded, tedious task. However, if you translate the roman numerals into the Arabic numerals we commonly use, the task becomes a whole lot easier. In this comparison, the process of translating of the roman numerals into the same Arabic numerals would take the role of the Fourier transform.

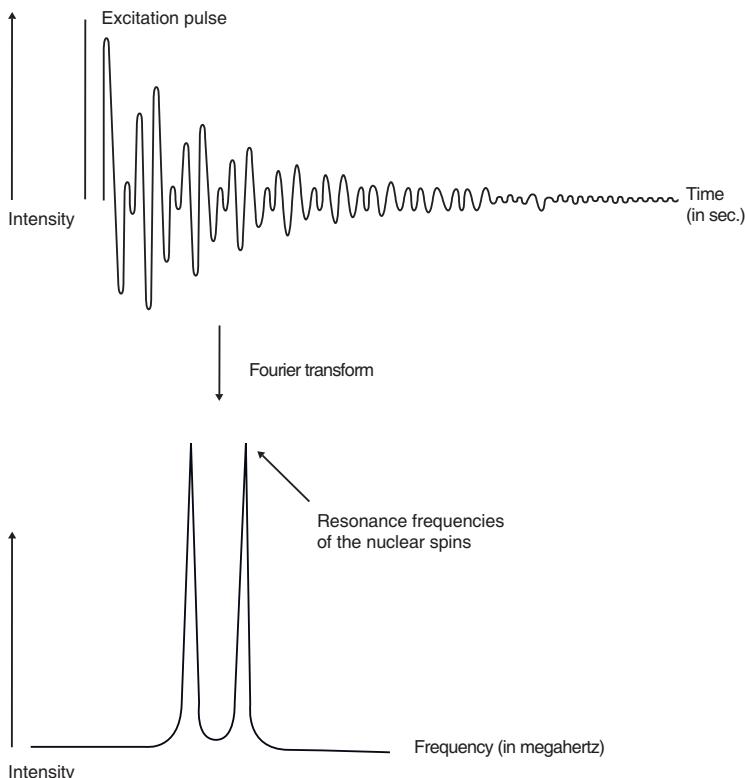
Pulse FT NMR method

A distinction is made between the continuous wave and the pulse FT NMR methods. With the continuous wave NMR method, the frequency of the radio waves sent to the sample is slowly changed so as to reach the resonance frequencies of the various nuclear spins one after the other. By contrast, with the pulse FT NMR method, a strong broadband radio wave pulse is sent to the sample, which covers the resonance frequencies of all the hydrogen nuclei in the molecule at the same time and allows these frequencies to be measured. This results in a superposition of signals, which can be decoded using the Fourier transform and converted into an NMR spectrum that can be easily interpreted. The advantage of the pulse FT NMR method is that it is up to 1,000 times faster than the previously used continuous wave method. Modern NMR equipment now only uses the pulse FT NMR method.

The Fourier transform

How a diffuse wave signal becomes a sharp frequency spectrum.

Example: Fourier transform in the NMR experiment



The measured electromagnetic signal, a wave function, is composed of the signal of all excited hydrogen atoms. By applying the Fourier transform, the individual resonance frequencies of the different nuclei can be filtered out and plotted along a frequency axis.

Figure 3 Example of a Fourier transform.

Noise

In principle, “noise” is the same in both the fields of acoustics and electronics: A mixture of waves or wavelets comprising electromagnetic or other waves with many different frequencies. We refer to “white noise” when it contains or is received at all the

frequencies within a certain bandwidth. Because NMR experiments on a subatomic scale have to measure extremely low signal strengths, any background noise can disturb the signal.

Signal/Noise ratio

The ratio between the signal and the noise is a measure of how sensitive an NMR device is. The sensitivity of the measurement depends on how clean the sample is, the strength and stability of the magnetic field, and the way the signals are analyzed. Various technical processes are used to ensure optimum conditions. The test tubes can be rotated quickly, for example, to ensure the sample is mapped homogeneously. The magnetic field is stabilized and systemic fluctuations can be corrected retrospectively by using a computer program. Parts of the noise may be eliminated by electronic filters. All of this helps to optimize the signal/noise ratio. The experiment can also be repeated as often as required, with the results being calculated based on the average readings from all the experiments. The latter decisive improvement is achieved by applying the pulse FT method, which makes it possible to accumulate more experiments within a given total measurement time.

2D NMR

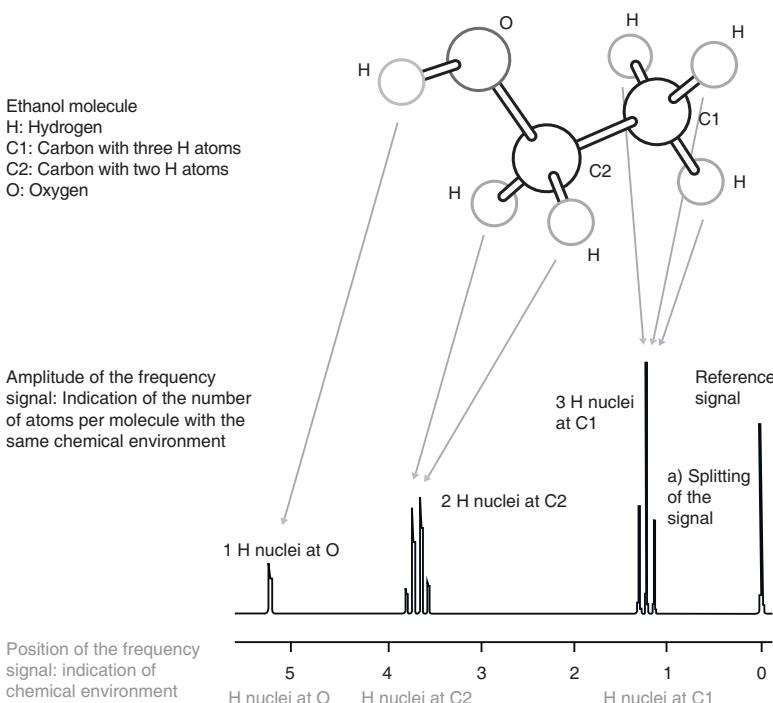
The two-dimensional NMR methods represents an enhancement of the procedure used to determine the structure of extremely large molecules comprising fifty or more atoms – natural proteins or DNA, for example. These molecules contain many different types of hydrogen atoms (with different chemical environments), which result in an extremely complex NMR spectrum with many overlapping resonance frequencies. A simple NMR measurement is therefore no longer sufficient. With the 2D NMR method, the hydrogen atoms in a molecule are excited with a radio wave pulse twice in succession. The response of the hydrogen atoms measured after these pulses differs according to their position in the molecule and their chemical environment, and depending on the time interval between the two pulses. The two dimensions refer to the time interval between the radio wave pulses, which is systematically varied as part of the

experiment. The advantage of this double excitation is that the differences between the hydrogen atoms in terms of their chemical structure and position are being “amplified”, which means that the various atoms and their positional and chemical relationships can be better identified.

The NMR spectrum

Where the clues to the structure of the molecule are hidden.

Example:
High-resolution NMR spectrum of ethanol
(measurement of hydrogen nuclei)



a) Splitting rule of frequency signals:
Indication of number of H nuclei bound to carbon atoms neighboring to the one considered.

Triplet signal: Each H-nucleus at C1 interacts with 2 H-nuclei each at the neighboring C2.
Quadruplet signal: Each H-nucleus at C2 interacts with 3 H-nuclei at the neighboring C1.
Singlet signal: H-nucleus at O has no interaction with other H-nuclei.

Figure 4 Model spectrum for ethanol and information that can be deduced from it.

Multidimensional NMR experiments

If three or more consecutive radio wave pulses (pulse sequences) are sent to a sample, the 2D NMR method can be expanded in various ways or into three or more dimensions.

MRI

MRI stands for magnetic resonance imaging (also referred to as magnetic resonance tomography, MRT). This medical imaging process is based on the same basic principle as the NMR method used in chemical analysis. An MRI device also aligns the nuclear spins of hydrogen atoms in a magnetic field and excites them using radio waves. In a body, it is mainly the hydrogen atoms found in water that are excited. However, an intricate technique is required to produce a three-dimensional image: In addition to a basic magnetic field, a linearly (gradually) increasing magnetic field is applied sequentially along each of the three physical axes, a “gradient”. Because hydrogen atoms in a weaker magnetic field give off signals at a lower resonance frequency than atoms in a stronger field, the signal measured in a body can be precisely located. The MRI process measures one sectional plane after the other, and the results are then converted into a three-dimensional image. Various technical processes and optimizations, for which several Nobel Prizes have been awarded, mean the process is nowadays both quick and reliable.

Tissue differentiation

There are three parameters that determine the brightness of a tissue in an MRI image and therefore the contrast: 1. The density of the hydrogen atoms; 2. The time that passes between the nuclear spin receiving one pulse and it becoming excitable once more; and 3. The time it takes for the signal to fade away after the atom is excited. All three of these factors vary depending on the tissue, and it is this variance that opens up the diagnostic potential of the MRI method. When carrying out measurements, the parameters can be set such that the different properties are expressed to a greater or lesser degree and the organs can be clearly identified. This makes it

possible, for example, to differentiate between white or gray brain matter, muscles, cartilage or even tumors and other tissues based on their characteristics without having to use contrast agents.

Functional MRI (fMRI)

The fMRI method represents a further development of the MRI method, which has allowed unimaginable progress to be made in the area of brain research, in particular. Japanese scientist Seiji Ogawa laid the foundations for this approach in the early 1990s. Unlike the MRI method, the fMRI method does not detect tissues or organs, but instead blood flows in the brain, given that increased brain activity increases oxygen demand in the relevant region. Hemoglobin is an iron-containing protein, which is loaded with oxygen as it passes through the lungs and then transports the oxygen in the blood. When a region of the brain is active, the ratio of oxygen-transporting hemoglobin to unloaded hemoglobin in the corresponding blood vessels is higher compared to inactive regions. It is possible to measure this difference as loaded hemoglobin has different magnetic properties to unloaded hemoglobin, and thus impacts the nuclear spin signals. This is known as the BOLD (blood oxygen level-dependent) effect.

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In the last 130 years, 30 Swiss people have won a Nobel Prize, and one of them is Richard R. Ernst. He laid the foundation for magnetic resonance imaging (MRI), which revolutionized medical diagnostics across the globe. In his autobiography, which the scientist completed shortly before he passed away at the age of 87, he talks about his life.

Prof. Ernst grew up in a family long-established in Winterthur, Switzerland, however his childhood and adolescence were overshadowed by a demanding father. He talks in detail about the start of his career in the 1960s, when he made a number of key discoveries at Varian Associates, Palo Alto, USA, as well as about his return to ETH Zürich, Switzerland, and the shark tank that university research is. The highly talented chemist reveals how his passion for Himalayan art began while travelling in Nepal, which ended in him building up one of the most significant collections of thangkas – the tantric Buddhist scrolls. In this book, Prof. Ernst discusses openly and directly about all aspects of his life, with humility and a wry sense of humor.



Richard R. Ernst (14 August 1933 – 4 June 2021) was a Swiss physical chemist and Nobel Laureate. He was awarded the Nobel Prize in Chemistry in 1991 for his contributions towards the development of Fourier transform nuclear magnetic resonance (NMR) spectroscopy while he was at Varian Associates, and the subsequent development of multi-dimensional NMR techniques. These underpin applications to chemistry with NMR spectroscopy and to medicine with MRI. He was professor of physical chemistry at ETH Zürich from 1976 until his retirement in 1998 and led a research group working on magnetic resonance spectroscopy.



Matthias Meili, born 1966, is a freelance journalist and author since 2018. He completed his undergraduate and master's studies in biochemistry from ETH Zürich. He was a science editor at major Swiss newspapers, such as *Weltwoche*, *NZZ am Sonntag* and *Tages-Anzeiger*, from 1998 to 2018. His work focuses on scientific research and the history of science. After Prof. Ernst told him about his fascinating life in long conversations, the decision for a fruitful collaboration for this book was quickly made.