At the very beginning the phenomenon of nuclear spin resonance was studied predominantly by physicists and the application was relatively limited. However, the discovery and understanding of chemical shift, which is the difference between resonance frequency of various structure units, made it possible to employ this method in chemistry as an analytical tool to describe structure of small organic molecules. With the development of the advanced experimental procedures, and hardware of spectrometers, NMR spectroscopy became unique method for structural biology to describe structure and dynamics of complex biomacromolecules. Nowadays many applications can be find in industry (pharmaceutical industry), metabonomic research, material engineering etc. But one of the most important current application is magnetic resonance imaging – very powerful diagnostic method.
Although the spin, the property of many particles, has not entire macroscopic analogy in many cases it can suggest rotation. Rotation and spinning is very common motion around us. But in contrast to macroscopic objects which can rotate around a rotation axis and gradually and fluently change their angular momentum, the energy states of spins are quantized, and all states and transitions, eigenvalues and eigenvectors are thoroughly described only by quantum mechanics.

Approximately 13 billion years ago large amount of energy was converted to the matter during the process known as The Big Bang. And from these times say from the Hadron or Electroweak epoch all fundamental particles, elementary particles and composite particles including protons and majority of heavier atomic nuclei possess mass, charge and spin. The internal nuclear spin was for the first time predicted by Wolfgang Pauli in 1924 as the fourth quantum number.
In quantum mechanics, nuclear spin can be expressed as angular momentum which is related to nuclear magnetic moment. In the static magnetic field orientation of nuclear magnetic moment is not stable but it is continuously changing. This leads to the well-known precession of spins. The spins rotate around the direction of magnetic field on a cone. Frequency of this rotation is the well-known resonant frequency. This means that the frequency of the excitation field must be exactly the same to successfully perform NMR experiment.

Spins placed into the magnet rapidly orientate into the two possible directions (parallel and anti-parallel), and originally degenerated energy level splits. In NMR experiment we observe transitions between these levels. Transition is induced by a pulse of rf field with frequency close to Larmor frequency. The difference in population at the energy levels determines the sensitivity of the experimental method. As you may see the sensitivity is very low and this is the crucial problem of NMR spectroscopy.

In principle majority of all nuclei can be considered as NMR active because they possess nuclear spin, however, we can easily use only those with nuclear spin one-half. This follows from the fact that these nuclei can exist only at two energy states (levels), and because we observe transitions between these levels, the resulting NMR spectrum is relatively narrow and easy to understand. The nuclei with higher-number-spin can be found at larger number of energy levels and consequently we observe a wide range of transitions and the resulting NMR spectrum is complicated and broad.
Theoretically it is possible to cool-down the samples, however in practice this procedure is limited by freezing points of solvents or low solubility, possible phase transitions etc. That is why the second way how to increase the sensitivity of NMR experiments is much better and this is general way which is usually used. On the other hand this way is very expensive.

For instance, the difference given by Boltzmann distribution in a collection of 1 million spins at the magnetic field about 2T is only 16. In general this difference increases with decreasing temperature and increasing magnetic filed.
Probably it will not be surprising that NMR spectroscopy can be also considered as a certain consequence of the research development in radar technology during the Second War. And that is why one of the first signals of water was observed early after the war at 1949 by Felix Bloch. Approximately ten years after he and E.M. Purcell were awarded by Nobel Prize.
A bit better version.

NMR spectrometer with a cryomagnet.
A current routine, everything is automated.

Research laboratories are equipped by several huge spectrometers with very high intensity of magnetic fields.
At the beginning of any NMR experiment there is nothing. There is no macroscopic magnetization, there is no precession as well. However, the spins placed into the strong magnetic field became oriented and start to rotate around the static magnetic field. The sum of all the vectors of nuclear magnetic moment produces longitudinal magnetization. However, this magnetization cannot be detected. That is why the system must be perturbed. The spin systems is irradiated by a very short radio-frequency pulse. This leads to the phase coherence in the rotation of spins around the magnetic field. The spins start to rotate at the same time from the same orientation. Consequently the vector summation produces transverse magnetization. Right this magnetization contains required information about the structure of molecules.

The transverse magnetization rotates around the magnetic field with the frequency which is close to theoretical Larmor precession frequency. In the detection coil a voltage is induced and subsequently recorded as so called Free Induction Decay. This FID contains all structural information, however, we are not able to understand it, we cannot read it. The clue to this problem gave Joseph Fourier in late 18 century. His mathematic procedure, Fourier transformation, converts the time functions to the functions of frequency. Almost two hundred years later this transformation was used by Richard Ernst to convert FID in to the form of a classical frequency spectrum. In the resulting spectra it is then possible to resolve individual structure units in molecules. These spectra can be understood as unique pictures of molecular structure. The main job of NMR researchers is a conversion of these spectra to a 3D model of the molecules.
Why can we resolve individual atoms in molecules? This possibility follows from the presence of electron clouds around each nucleus. Electrons in magnetic field produce very weak magnetic fields which can increase or decrease the intensity of static magnetic field produced by the magnet. That is why the nuclei are placed in so called effective magnetic field and due to this fact frequency of the precession of transverse magnetization is slightly affected. We can observe differences in precession frequencies for different atoms. For instance, increasing electronegativity of a neighboring atom increases value of the chemical shift. Simply speaking position of signals in NMR spectra strongly depends on the electron density around the investigated atoms.

However, one crucial problem follows from the fact that the differences between resonant frequencies of various nuclei are very small. In many cases it is necessary to resolve two signals differing in frequency by only 0.1Hz. This is very complicated.
Nevertheless solution state NMR have become routine technique to characterize organic molecules. Thanks to fast isotropic molecular tumbling only isotropic values of chemical shift are detected and all molecules in the solution are equivalent. Consequently the resulting NMR spectra are highly resolved with line-width usually below 0.1 Hz. Ideally every structure unit in the molecule is resolved and characterized by its own chemical shift.
The situation should be the same also in polymer systems, however there are some differences. Clear and well defined multiplicity rapidly disappears and at the same time signals became broader and broader as a result of increasing molecular weight and viscosity of solution. Narrow signals then reflect low-molecular-weight impurities. However, shorter oligomers still exhibit high-resolution pattern. Standard one-dimensional experiment performed on copolymer polypeptide-polyethylene oxide produces traditional $^1$H NMR spectrum. One can see residual signal of water and signals reflecting traces of residual ether. Polyethylene oxide block is reflected by the main signal and several low intensive signals correspond to the nonequivalent terminal units. These terminal units can be found also for polypeptide block. The spectrum then provide information about the basic structure, composition and purity of the polymer systems.

Typical $^1$H NMR spectrum contains four basic parameters. i) The number of signals - this should corresponds to the number of basic structure units. ii) Then the signal intensity - this should reflects the number of equivalent hydrogen atoms in one structural group. iii) The position of signal on NMR scale - this is the previously mentioned chemical shift. Here we can see typical values of chemical shifts of basic units. iv) And finally this is the multiplicity of signals. This is the number of signals in the multiplet which reflects the number of hydrogen atoms in the neighboring function groups.

$^1$H NMR spectra (basic parameters)

1. Number of signals.
2. Integral intensity (depends on number of atoms in one structure unit).
3. Chemical shift (position of signal depends on chemical surrounding).
4. Multiplicity (signals have fine splitting which depends on the number interacting spins).

$^1$H NMR spectra and polymers

1. Multiplicity rapidly disappears.
2. Signals are broaed with increasing molecular weight.
3. Determination of primary structure, composition and purity.

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Unambiguous signal assignment can be achieved by two-dimensional spectroscopy. Simply speaking, to obtain 1D spectrum one response of the sample to at least single pulse during one detection period must be detected. The acquisition of 2D spectra requires detection of the response of a sample to at least two pulses during two detection periods. In practice a series of 1D spectra with gradually prolonging T1 period is recorded. As magnetization evolves after the first pulse, the intensities of signals detected during the second period are modulated by the length of this period. In fact the intensities of these signals oscillate. Consequently the second FT of this oscillation produces a two-dimensional spectrum. First of all this spectrum significantly enhances spectral resolution. Information originally stored in one dimension are expanded on the plane.

For peptides and proteins the position of signals of α-protons also reflects secondary structure, the conformation of the backbone. In principle it is relatively easy to resolve α-helix or β-sheet. There is a large database containing values of chemical shifts and there are tables of these values for random coil unfolded structures. Deviation from these random coil range toward higher values indicate formation of β-sheet conformation while deviations toward lower values rather indicates formation of α-helix. This procedure is known as the Chemical Shifts Indexation (CSI).
In general we proceed by the method trial-and-error. At first we must at least assign one signal for instance the CH proton with double bond. We find the correlation signal reflecting the neighboring proton number 10 than proton number 9 and so on and so on. It seems to fit well with our assumption. In general we try to start from well defined signal of structure unit with extraordinary chemical shift. Owing to we can trace proton-proton interaction network with steps which are long only three chemical bonds. That is why we can describe primary structure or topology of molecules. However, some times the interaction network is broken and in many cases the resolution in this region is very poor. That is why we need additional increase in the spectral resolution.

What can be seen in the 2D spectrum? And what is the interpretation of the signals? Diagonal signals directly correspond to the signals which are detected in 1D spectrum. However, if information about the polarization state of a hydrogen atom in one structure unit is transferred to the neighboring hydrogen atom than the off-diagonal signal appears. Such information or polarization is transferred via bonding electrons and the longest distance is 3 or 5 chemical bonds. For instance starting from the signal which probably corresponds to Val methyl protons, the off-diagonal signal correlates with the structure unit which is connected via three chemical bonds. So by this way we found out the signal of CH beta hydrogen and subsequently the other correlation signal indicates alpha proton. This procedure must be repeated for all signals. And by this way complete assignment of all signals in the 1H NMR spectra can be performed.
During 70’s and 80’s last century, NMR researchers learned to manipulate with the spin systems so skillfully that they could obtain detailed information about interatomic distances, local geometry and segmental dynamics of a wide range of materials and natural products. Owing to this manipulation which is sometimes called as spin-gymnastics, the advanced techniques of NMR spectroscopy allow us to determine the global structure of proteins, nucleic acids and their complexes in solution.

One of the most outstanding scientists which significantly developed these techniques is Kurt Wüthrich which was awarded the Nobel Prize in 2002. Consequently, NMR spectroscopy crossed a borderline of physics and chemistry and became an inseparable part of structural biology.

To increase spectral resolution very often NMR spectra of other nuclei especially of carbon 13 are measured. As you can see the signals are well separated and every carbon atom is reflected by a single signal. It is very good, in general it is true that with increasing number of electrons around a nucleus the dispersion of chemical shift increases. On the other hand this experiment is less sensitive because the isotopic abundance is only 1%.
At present the main research interest is focused to biologically active macromolecules with limited solubility. At first this is concerned to the membrane peptides and proteins which control wide range of biological processes in living cells. For instance stabilization of membrane potentials, regulation of cell volume or transport of ions etc. The second type of the interesting systems provides amyloid proteins and Prion-related proteins. It is very difficult to prepare suitable single crystals of these membrane proteins or convert these membrane proteins to a solution. In this case just only solid-state NMR spectroscopy can provide required structural information.