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NMR at low magnetic fields

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ABSTRACT

NMR provides outstanding information in chemistry and in medicine. But the equipment is expensive as high-field magnets are employed. Low-field NMR works with inexpensive permanent magnets. Until recently these did not provide fields sufficiently homogeneous for spectroscopy and were mostly used for relaxation measurements. Relaxation can also be measured outside the magnet, and small mobile NMR devices have been developed for non-destructive testing of large objects. Today small stray-field magnets and small magnets with homogeneous fields are available for relaxation analysis, imaging, and spectroscopy. Their availability is believed to be essential for shifting NMR analysis from a specialist's tool to a convenience tool.

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1. Introduction

The familiar trend followed by consumer electronics is that the devices become smaller and more powerful with time. Examples are cell phones (Fig. 1a), computers, and data storage devices. This trend is countered in NMR [1,2] by the introduction of ever stronger magnets in recognition of the common belief, that only higher fields lead to better instruments, as sensitivity and chemical shift dispersion increase proportional to field strength. Strong magnets are large and expensive so that fewer and fewer institutions can afford the space and the money for top-of-the-line NMR instrumentation, and access to high-field NMR equipment is the privilege of a shrinking number of scientists. Moreover, today's NMR magnets are expensive to maintain, as they are made from super-conducting coils that require permanent cryogenic cooling.

Whereas NMR magnets with field strengths in the 1–5 T range were common in the early days of multi-dimensional NMR, the major NMR instrument manufacturers do not produce such instruments anymore, as they exhibit inferior performance in NMR spectroscopy of large molecules and low concentrations. Nevertheless, the past years have witnessed the advent of small NMR magnets from permanent magnet material (Fig. 1b), so that small NMR devices with field strength up to 2 T are now being realized, that do not require cryogenics, are highly mobile, and are inexpensive [3–10]. The widespread availability of such NMR equipment may change the image of NMR: the low price and the small size enable the use of NMR for applications prohibited by or difficult to perform with high-field machines. These applications can be grouped into three categories: high-throughput applications by parallel use of many devices or with permanently installed sensors, applica-

tions at the site of interest which are enabled by the mobility of the small instrument, and applications in dangerous environments such as under a chemistry hood, in clean rooms, in high pressure labs, danger zones of explosive and radioactive substances.

The trend to develop magnets with higher field strength, familiar from the evolution of super-conducting magnets, is likely to be followed also with modern permanent magnets. While the upper field strength of permanent magnets is limited by the availability of suitable materials for magnets of small size, lower fields present other opportunities. At high field, the NMR spectrum is simple, as the Zeeman interaction of the spins with the polarizing magnetic field dominates all other spin interactions. At zero magnetic field, only the internal spin interactions provide the magnetic field required to observe nuclear magnetic resonance, and the spectrum is also simple [11]. At intermediate field strengths, where the Zeeman interaction and the interactions between spins are of similar magnitude, the NMR spectra are most complicated, and many lines are observed [12–15]. This strong-coupling limit may seem like a nuisance for spectral analysis, but the spin system therein reveals a maximum of information. The spin states show maximum entanglement, so that this regime may be of interest not only for chemical analysis, but also for fundamental studies in quantum computing.

The obvious disadvantage of NMR at low magnetic fields is the inherently low sensitivity due to the small differences in the thermodynamic equilibrium populations of the spin states, leading to low longitudinal magnetization and the low precession frequency of the transverse magnetization. This disadvantage can be overcome by different hyper-polarization techniques, which polarize the nuclear spins beyond their thermodynamic equilibrium populations [16–24] and by methods of detection alternative to nuclear induction which are more sensitive at low precession frequencies of the transverse magnetization [11,25–39].

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Fig. 1. Examples of miniaturization. Progressing miniaturization goes along with increased functionality. (a) Telephones. (b) NMR magnets for high-field NMR (left) and low-field NMR (right). The spectrum on the screen is from toluene in a 2 mm diameter sample tube acquired at 30 MHz with the magnet shown on the right [3,4].

Along with the advances in down-sizing the spectrometer electronics to a single chip [34,35] and using micro-coils [36–39] or alternative schemes for detection [25–33], small table-top NMR is already apparent the horizon (Fig. 1b), while cell-phone-size NMR devices are envisioned as a tool for screening assays of body fluids [6,34,40] and as a personal convenience tool to monitor skin, for example. In the following, developments of NMR at low magnetic field are featured from a personal perspective, outlining major development and application areas. While a structure according to the three identified application regimes, high throughput, mobility, and dangerous environments is most desirable, the different types of magnets and measurement principles need to be understood first. For the sake of brevity, representative applications are addressed together with the different types of magnets and the principal types of measurements.

The measurement types are [41] NMR relaxation measurements (NMR relaxometry), which poses the least demands on magnetic field quality, NMR imaging, which favors magnetic fields linear in space with a constant gradient, and NMR spectroscopy, which requires highly homogeneous fields. These demands on magnetic field quality can be fulfilled with closed magnets [3–7,9,10,42] similar in shape to the super-conducting magnets which accommodate the sample inside, but also with open magnets [3,4,8–10,43,44], where the object is exposed from one side to the stray-field of the magnet. The latter geometry permits objects of any size to be analyzed non-destructively, and portable stray-field NMR sensors like the NMR-MOUSE® [45,46] are interesting tools for non-destructive testing in a wide range of applications [9].

2. Measurement methods

NMR is a resonance phenomenon between magnetization of nuclear spins and magnetic radio-frequency (rf) waves [1,2,47]. It is utilized to investigate molecular properties of matter. The strongest magnetization from stable nuclei is from protons, which also exhibit the highest resonance frequency in a magnetic field of given strength. This is why protons show the highest sensitivity and are most frequently investigated by NMR.

The relationship between the amplitude B_1 of the magnetic rf field and the measured magnetization response $s(t)$ is nonlinear, as longitudinal magnetization $M_z(t)$ is interchanged with transverse magnetization $s(t) = M_x(t) + i M_y(t)$ for measurement by a rotation of the magnetization vector $\mathbf{M} = (M_x, M_y, M_z)^T$ with an rf impulse. The measurement concepts of NMR, therefore, are particular realizations of nonlinear systems analysis adapted to the specific features of nuclear spin systems. In systems analysis, it is common practice to measure the impulse response, known as the free induction decay (FID) in the NMR community, which consists of a decaying oscillatory function (Fig. 2a). When measured in a homogeneous magnetic field, the oscillatory and the decaying parts of the impulse response provide chemical and physical information, respectively. In a homogeneous field, all voxels of the sensitive volume that covers the sample experience the same

characteristic magnetic field B_0 , and magnetization components in different voxels interfere constructively, as all coherently oscillate with the same resonance frequencies $\omega_0 = 2\pi\nu_0 = \gamma B_0$. The frequency distribution of the oscillating part of the impulse response is displayed in the NMR spectrum, which is the Fourier transform of the impulse response function. It is the prime source of information for molecular structure determination in chemical analysis. The envelope of the impulse response function in a homogeneous magnetic field is known as the transverse relaxation function. For simple liquids, this decay is exponential with a time constant T_2 ,

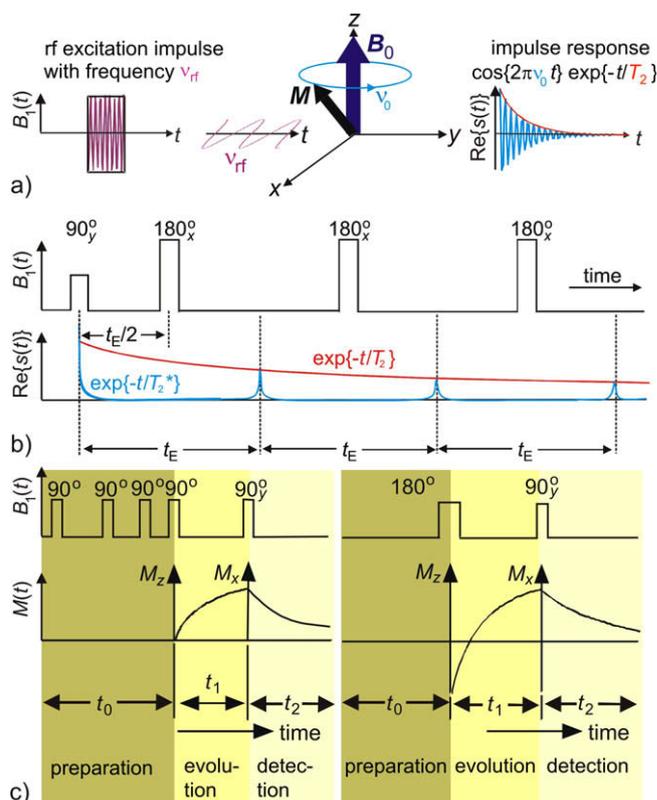


Fig. 2. [47] Basic measurement schemes in NMR with impulse excitation. (a) The NMR response is invoked with an impulse of an oscillating, magnetic rf wave with amplitude B_1 the frequency $\omega_{rf} = 2\pi\nu_{rf}$ of which matches the precession frequency $\omega_0 = 2\pi\nu_0 = \gamma B_0$ of the transverse magnetization in the magnetic field B_0 . The impulse response is measured. It is converted into a distribution of relaxation times by Fourier transformation or the envelope of the impulse response is converted into a distribution of relaxation times by inverse Laplace transformation. (b) The envelope can also be sampled in an inhomogeneous magnetic B_0 field by a train of echoes which are generated from the impulse response by multiple 180° rf impulses separated by the echo time t_E . (c) The relaxation time T_1 for build-up of longitudinal magnetization M_z is measured indirectly by observing the momentary value of M_z repetitively at different times t_1 in terms of the amplitude of an impulse response or a CPMG echo train acquired during t_2 . Initially, the longitudinal magnetization is destroyed (left) or inverted (right) in a preparation time t_0 .

known as the transverse relaxation time. For multi-component decays, the distribution of relaxation rates $1/T_2$ is given by the Laplace transform of the relaxation function. It is typically displayed on a logarithmic scale, and only three to four peaks can be resolved in NMR. The logarithmic distribution of relaxation times is the prime source of information in NMR relaxometry. Relaxometry is mostly used in well-logging NMR, where the fluids in the porous wall of the bore of a well are analyzed with stray-field NMR devices that are inserted into the hole [48,49].

In an inhomogeneous magnetic field, ω_0 varies across all voxels, the magnetization components interfere destructively, and the impulse response decays faster than in a homogeneous field. The growing phase differences between magnetization components that evolve with different resonance frequencies can be reversed with a 180° impulse that effectively changes the sign of the resonance frequencies of the transverse magnetization. The use of a second impulse in the excitation leads to the NMR echo discovered by Hahn in 1949 [50]. By appending further 180° impulses to the excitation, a string of echoes can be measured, where each echo stroboscopically probes the envelope of the impulse response function in homogeneous field (Fig. 2b). This excitation scheme is basic for NMR in inhomogeneous magnetic fields. The excitation sequence is named CPMG sequence, paying tribute to its discoverers Carr, Purcell, Meiboom and Gill [51,52]. In strongly inhomogeneous fields, longitudinal and transverse magnetization components become mixed in a CPMG sequence, so that effective relaxation times $T_{2\text{eff}}$ are extracted from the CPMG decay and not the exact values of T_2 observed in homogeneous field [53,54].

While the relaxation time T_2 is associated with the irreversible loss of transverse magnetization, the longitudinal relaxation time T_1 is the time constant for formation of thermodynamic equilibrium magnetization by aligning the nuclear spins in a magnetic field. This magnetization build-up is measured in an indirect way. First the longitudinal magnetization M_z is destroyed or inverted (Fig. 2c). Then its return to equilibrium in an evolution time t_1 is probed by converting the longitudinal magnetization into transverse magnetization with a 90° impulse to measure the impulse response or the transverse magnetization decay with a CPMG sequence. The initial amplitude of either signal reports the value of $M_z(t_1) = M_x(t_2 = 0)$ while the signal is acquired as a function of the detection time t_2 . This measurement scheme of indirect detection introduces the concept of multi-dimensional NMR [2,55].

Multi-dimensional distributions of frequencies and relaxation times are the Fourier and Laplace transforms, respectively, of multi-dimensional time functions produced by experimental schemes that systematically manipulate the initial magnetization of the signal $s(t)$ and which are detected either as an impulse response or a CPMG echo train (Fig. 3). The general 2D scheme [55] starts with thermodynamic equilibrium magnetization M_0 which is produced in a waiting time of the order of $5T_1$ before the first rf excitation impulse. This impulse is usually a 90° impulse which generates a maximum in the transverse magnetization. Each magnetization component oscillates with its own frequency ω_0 and decays with its own time constant T_2 . Another 90° impulse converts the x or y projections of these transverse magnetization components at time t_1 to longitudinal non-equilibrium magnetization components, which partially return to equilibrium in a mixing time $t_m < 5T_1$ under the influence of different spin–spin interactions and molecular motions. These interactions and motions may mix the magnetization components so that some assume a different frequency or relaxation time in the subsequent observation period t_2 . If the maximum values of t_1 and t_2 are short compared to the mixing time t_m , this scheme measures joint probability densities that a magnetization component is found in a state characterized by ω_{01} or T_{21} in the short time interval t_1 , and in a state characterized by ω_{02} or T_{22} in the short time interval t_2 some time t_m later. Depending on t_m , and proper manipulation of the experimental conditions during the evolution, mixing and detection times, spectral, spatial, relaxation, velocity, and diffusion information can be correlated. Such schemes are most powerful in providing detailed insight into the spin system that often cannot be derived from the simple impulse response alone. In fact the response to multiple rf impulses probes the nonlinear properties of the system, and multi-dimensional NMR is one from of nonlinear systems analysis [2,56,57].

3. Small NMR magnets

There are two principal types of NMR magnets, of closed or open design. Closed magnets accommodate the dedication volume inside the magnet bore (Fig. 4a) and open ones outside (Fig. 4b). High field strength and homogeneity are easier to achieve with closed geometries, while large objects are easier to investigate with open geometries. Either design can be miniaturized when

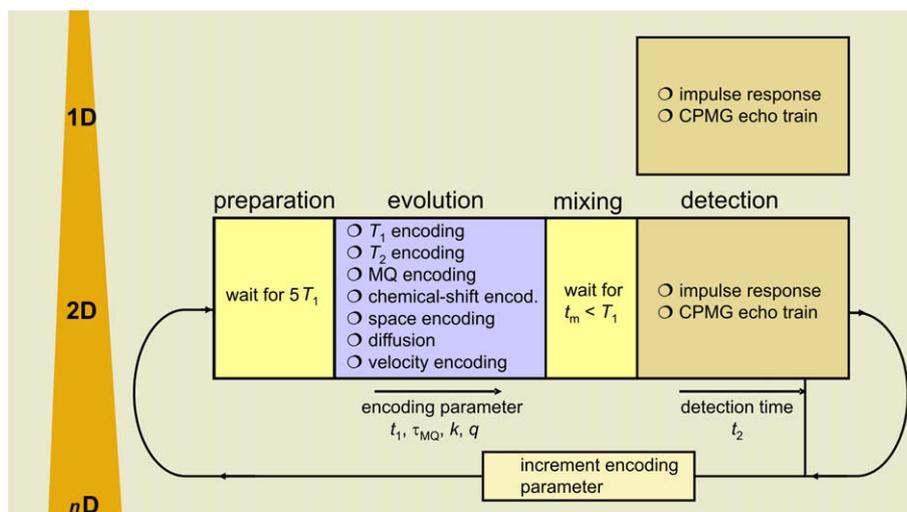


Fig. 3. Multi-dimensional NMR. Typically, an impulse response or a multi-echo CPMG train are detected directly. In 2D NMR its initial amplitude is modulated by spin manipulations during the preceding evolution time t_2 and mixing time t_m for indirect detection of information on chemical shift (t_1), relaxation (t_1), multiple quantum correlations (τ_{MQ}), position (k ; imaging), displacement by coherent motion (q : velocity) and incoherent diffusion (q).

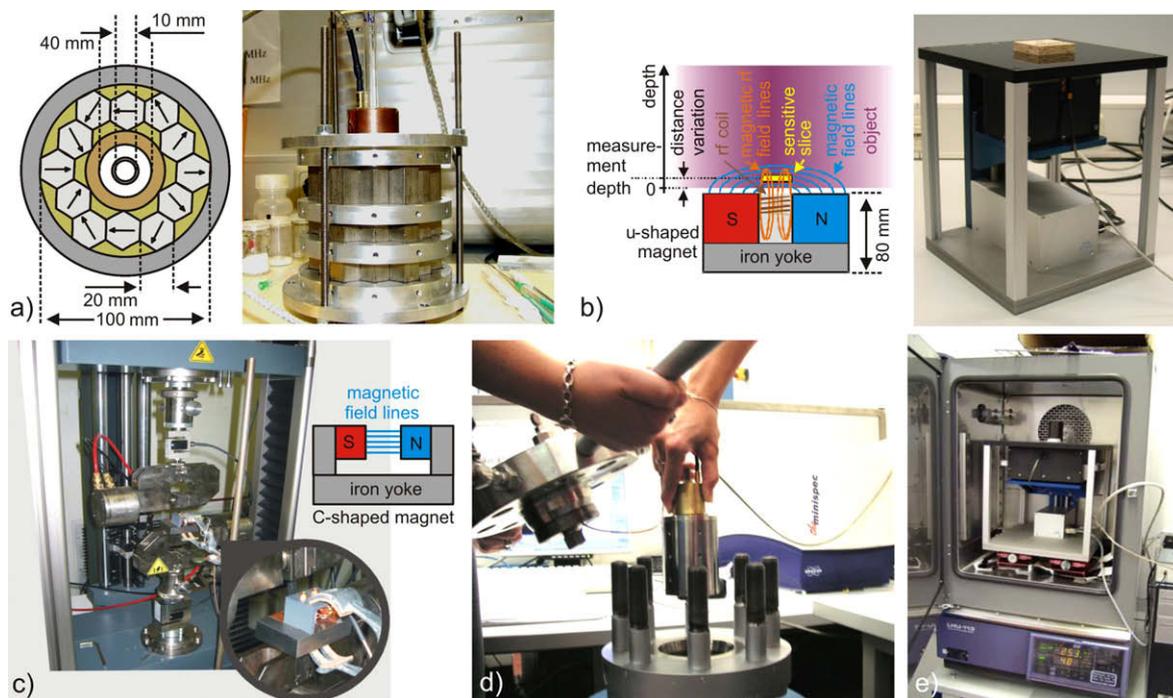


Fig. 4. Permanent magnets for NMR and their uses. (a) Halbach magnet. (b) NMR-MOUSE. (c) In-line monitoring of a stress-strain experiment by NMR with a classic C-shape magnet. (d) Insertion of a Halbach relaxometry magnet into an autoclave for NMR at elevated pressure. (e) Setup of an NMR-MOUSE[®] inside a climate chamber for temperature- and moisture-dependent relaxometry.

permanent magnets are employed, providing mobility and simplicity of maintenance. A particularly successful closed geometry is due to Halbach (Fig. 4a) [5,58]. Such magnets are cylinder-shaped with maximal magnetic field inside and ideally zero stray-field outside. The magnetic field direction is transverse to the cylinder axis so that a simple axial solenoid can be used as rf coil. The simplest open magnet is a horse-shoe magnet (Fig. 4b) that provides a stray-field parallel to the surface of the pole faces [59]. The rf coil is positioned inside the magnet gap, and the profiles of the stray-fields of both, the magnet and the coil define the position and the shape of the sensitive volume at a given transmitter frequency ω_{rf} .

Each type of magnet is built from blocks of permanent magnet material such as sintered FeNdB or SmCo material. The magnetization of such blocks varies by a few percent among similar blocks. On the other, hand magnetic field homogeneity of better than 10^{-7} is needed across the sensitive volume for NMR spectroscopy. To reach such homogeneity, super-conducting magnets and electromagnets are fitted with current-driven shim coils that generate magnetic fields with profiles following the different orders of the spherical harmonic functions to compensate the inhomogeneity of the main magnetic field. This approach cannot be used for small permanent magnets, as currents of hundreds of Amperes would be needed given the inhomogeneity of such magnets. The classical solution is to homogenize the field with precision pole shoes [60,61] and the use of shim coils to eliminate the residual inhomogeneity. But electrical shims require power cords and generate heat, which may lead to a field drift. A fundamental advance in magnet design therefore was the development of shim concepts that are based on adjusting the position of movable magnet blocks properly incorporated into the assembly of permanent magnet blocks so that magnetic fields sufficiently homogeneous for NMR spectroscopy (with better than 0.2 ppm spectroscopic resolution) can be obtained despite the low magnetic field precision of the individual magnet blocks. Such concepts have been shown to work for a sensitive volume inside a Halbach magnet [42,62], as well as

for the sensitive volume outside stray-field sensors [43,44]. In fact, by proper shimming, stray-fields locally homogeneous for spectroscopy and linearly space-dependent with different gradient values for imaging can be generated over an extended volume. By such techniques, magnets are obtained, that can be operated without power supply and are ideal for applications where the NMR set-up has to be moved to or operated in hitherto unusual environments, such as in a permanent installation as a sensor (Fig. 4c), in an autoclave for high pressure NMR (Fig. 4d) or inside a climate chamber (Fig. 4e) [3].

4. Types of measurements and examples

The three different types of NMR measurements, i.e. relaxometry with minimum demands on magnetic field quality, imaging with linear gradient-fields and spectroscopy with homogeneous magnetic fields, are illustrated in the following by one selected example for each, a Halbach magnet and a stray-field magnet.

4.1. Relaxometry

NMR relaxation curves can be measured with simple devices, as the magnetic field for data acquisition can be inhomogeneous. The NMR signal is detected in terms of echoes, typically Hahn echoes [45], or multiple echoes such as CPMG echo trains [46,47]. The signal amplitude for zero time is proportional to the spin density, given long enough recycle times for the spin system to reach thermodynamic equilibrium. If the recycle time is shortened, a longitudinal relaxation weight is introduced [63]. Such T_1 weighting can also be achieved by means of an inversion or saturation recovery sequence which precedes the multi-echo detection sequence (Fig. 2c).

Molecular translational self diffusion is measured easily and with high accuracy with stray-field sensors [9] like the Profile NMR-MOUSE[®] [46] that exhibit a linear field profile with a constant gradient across the sensitive volume. As the gradient of small

stray-field sensors is high, only short position-encoding times are needed to mark initial and final positions in displacement measurements, and relaxation effects can often be neglected [64].

The relaxation and diffusion curves are analyzed either by fitting model functions such as $s(t) = s(0) \exp\{-(t/T_2)^b/b\}$, which is a simple exponential function for $b = 1$ and a Gaussian function for $b = 2$ [9,65], by reducing the decay function to a contrast parameter such as $w = \int_0^{t_1} s(t) dt / (\int_{t_1}^{\infty} s(t) dt)$ by partial integration of the echo envelope decay $s(t)$ (Fig. 2b) [9], or by calculating distributions of diffusion coefficients or relaxation times by operations equivalent to inverse Laplace transformation of the measured signals. All these measurements can be conducted in inhomogeneous magnetic fields and expanded to multi-dimensional experiments (Fig. 3) [2,66,67].

4.1.1. Relaxometry inside a magnet

Relaxation measurements can be carried out with simple magnets in inhomogeneous magnetic fields by echo techniques (Fig. 2). The inverse Laplace transform of the echo train envelope is the distribution of relaxation times, which is often multimodal, with each peak identifying a specific relaxation environment. As of recently, relaxation measurements are being optimized for counting cells specifically labeled with ferromagnetic nano-particles and passing through a capillary inside a small magnet [6,7,34,40]. This type of NMR bears great promise for high-throughput analysis in biomedical research and routine use. Another area of application is in chemistry, where small magnets can be used under the exhaust

hood to monitor chemical reactions in small-scale set-ups, including micro-reactors, at elevated pressure inside an autoclave (Fig. 4d), at elevated temperature inside a climate chamber (Fig. 4e) [3,4], and in other conditions that are extreme on the scale of conventional NMR, such as NMR of explosives and radioactive substances.

Even with primitive Halbach magnets (Fig. 4a), two-dimensional (2D) relaxation–relaxation exchange experiments [68,69] can be conducted. For example, for water-saturated 500 nm diameter porous silica particles, the surface-bound water exchanges with the bulk water, and this exchange can be monitored by T_2 – T_2 exchange NMR (Fig. 3) as the two water environments have different transverse relaxation times T_2 [70]. Within a mixing time of $t_m = 70$ ms, the water molecules exchange between the two environments, as revealed by the cross-peaks in the exchange spectrum (Fig. 5a). These exchange spectra can be simulated in a straight forward way by collecting all magnetization components involved in the exchange process in a vector \mathbf{M} [2,71,72]

$$\mathbf{M}(t) - \mathbf{M}^{\text{eq}} = \exp\{-(\mathbf{R} + \mathbf{K})(t - t_0)\}[\mathbf{M}(t_0) - \mathbf{M}^{\text{eq}}], \quad (1)$$

where \mathbf{M}^{eq} is the vector at thermodynamic equilibrium, \mathbf{R} is the diagonal relaxation matrix which collects the longitudinal relaxation rates if \mathbf{M} represents longitudinal magnetization and the transverse relaxation rates if \mathbf{M} represents the transverse magnetization components, and \mathbf{K} is the kinetic matrix which collects the exchange rates between the magnetization components. By modelling exchange spectra acquired for different mixing times, the kinetic

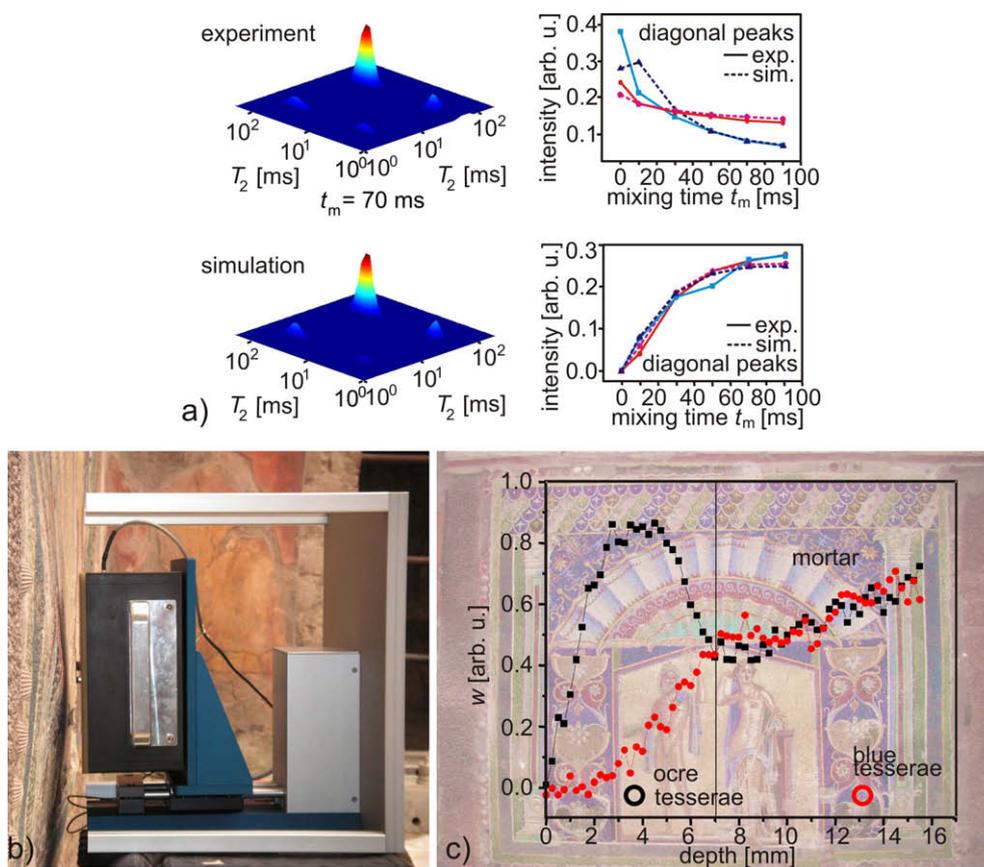


Fig. 5. NMR relaxometry. (a) 2D relaxation exchange NMR of water in contact with nano-porous silica particles measured in the Halbach magnet of Fig. 4a. From simulations of experimental t_2 – t_2 exchange spectra acquired for different exchange times t_m , the time evolution of the peak integrals can be followed to extract the relaxation times, T_1 and T_2 of the exchanging components and the kinetic constant k_{12} of the two-site exchange. (b) Profile NMR-MOUSE[®] with 25 mm depth access measuring the moisture in the mosaic of Netpune and Amphitrite in Herculaneum. (c) Depth profile of the weakly relaxation-weighted proton spin density w as a function of depth for ochre and blue tesseræ. The ochre mosaic stones show high and the blue ones low moisture content, while the moisture profile of the mortar embedding the tesseræ is the same at both locations.

constants of the exchange process can be extracted. This exemplifies that relaxation NMR is an attractive tool to study dynamic processes in chemical engineering and in the chemistry laboratory.

4.1.2. Relaxometry outside a magnet

The most important use of stray-field NMR with portable sensors is for depth profiling of layered objects [44]. Layered structures arise in a manifold of objects [8,9,73], such as composite packaging materials with barriers to block permeation with specific fluids or gases. Some examples are human skin [8,9], paint [8] and protective layers on diverse objects such as paintings, musical instruments, furniture, chip boards, and building materials. Layered structures can also develop in formerly homogeneous materials when exposed to aggressive environmental conditions or specific chemicals, such as drying textiles and paint layers, and fluids swelling a container wall.

In investigations of skin and objects of cultural heritage, the portability of the NMR device and the noninvasiveness of the technique are valuable assets. For example, a Profile NMR-MOUSE[®] with 25 mm depth access has been employed to investigate the moisture content of the world cultural heritage mosaic of Netpune and Amphitrite in Herculaneum (Fig. 5b) [74]. Moisture is a key concern in the conservation of the excavation site. Depth profiles measured at two positions through the mosaic reveal a large difference in moisture uptake of the tesserae and the same moisture profiles for the mortar embedding the mosaic stones (Fig. 5c). While applications of stray-field NMR to objects of cultural heritage are attractive, far wider use of the technique is expected with applications to the human body, like following wound healing underneath bandages, allergy studies and other medical studies of skin, and last but not least skin monitoring in personal cosmetic day care [3,8,9,73]. Here, stray-field sensors like the NMR-MOUSE[®] have the potential of becoming a routine or even convenience tool of analysis.

4.2. Imaging

The measurement of depth profiles is a form of one-dimensional imaging. Such profiles can be acquired with a depth resolution of better than 10 μm at the expense of reduced lateral resolution, of the order of 10 mm [46]. 2D and 3D imaging with compact NMR magnets is challenged by low-field strengths and corresponding low sensitivity. However, the field strength 0.5 T of early medical imagers can easily be reached with permanent magnet assemblies, such as Halbach magnets and the NMR-MOUSE[®]. With open stray-field sensors, it is more difficult to achieve good uniformity of the magnetic field for imaging across the sensitive volume than with magnets that enclose the object, so that closed magnet geometries are preferred over open geometries whenever possible.

4.2.1. Imaging inside a magnet

For imaging, the demands on field uniformity are higher than for relaxometry, and magnets with inhomogeneities, such as those encountered in simple Halbach magnets, need to be shimmed. Dedicated imagers with permanent magnets have been built for a variety of applications, such as plant studies, animal studies, and limb studies [9,75–78]. A portable Halbach magnet shimmed with permanent magnets to 10 ppm homogeneity across samples with diameters of 30 mm has been constructed (Fig. 6a) and tested for imaging of plants and fluid flow through a pipe [42]. Also, volume flow rates can be determined with great accuracy with such devices, and the velocity profile across the tube diameter can be measured (Fig. 6b) for analysis of non-Newtonian flow. Such magnets can also be employed to characterize flow velocities in the range from 0.1 mm/s to 5 m/s in metering applications of slow flow like intravenous drug delivery and product flow in a plant.

4.2.2. Imaging outside a magnet

Slice-selective 2D images have been obtained from a stray-field magnet similar to the Profile NMR-MOUSE[®], but fitted with coils that produce magnetic fields parallel to the main field with orthogonal gradients in the plane of the sensitive slice (Fig. 6c) [9,79,80]. In stray-field magnets, the field gradient perpendicular to the sensor surface may be several T/m, so that the sensitive volume is a thin slice, and the acquisition time for an image (Fig. 6d) may be many minutes up to one hour. As this is too long for practical applications, the slice thickness has to be increased by reducing the gradient. Other than by introducing shim magnets [43,44], this has been demonstrated to be possible with a tunable array of cylinder magnets magnetized transverse to their axes, each of which can be rotated by worm drives to adjust the shape of the sensitive volume, its size, and its position [81], to eventually acquire 3D images in Fourier mode by portable MRI in an emergency vehicle and in remote areas of human settlement.

4.3. Spectroscopy

Magnets for NMR spectroscopy place the highest demands on field homogeneity and field stability. Yet, Halbach magnets and stray-field magnets built from sintered FeNdB or SmCo blocks can be shimmed by iterative adjustment of magnet positions to produce a sensitive volume with good enough homogeneity for NMR spectroscopy [42–44]. The maximum field strength is above 1 T for Halbach magnets but less for stray-field magnets, as the sensitive volume is outside the magnet. Temperature drift of the magnets is an issue at this stage of development, but concepts for self compensation of temperature-invoked field drifts are being tested that explore the addition of two magnetic fields in the sensitive volume with temperature drifts that cancel each other. For NMR spectroscopy at very low magnetic fields, electromagnets

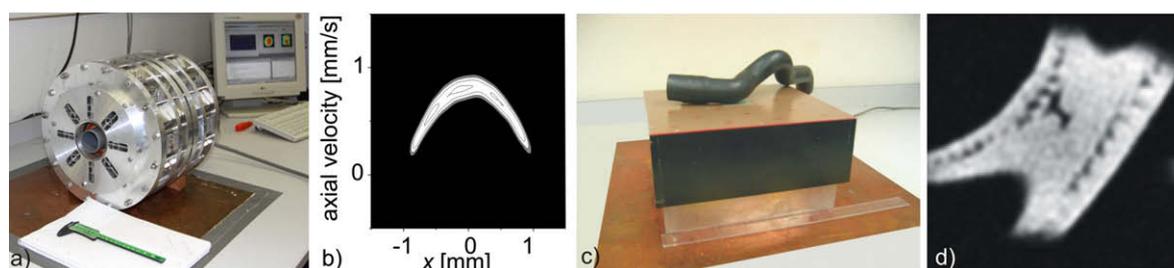


Fig. 6. Imaging. (a) Shimmed Halbach magnet for imaging of 3 cm diameter objects [42]. (b) Slice-selective velocity profile of water flow in a 2 mm inner diameter pipe passing through the magnet of Fig. 6a. The acquisition time was 1 min. (c) Stray-field scanner to image 2D slices parallel to the surface of the scanner. It is used similar to a magnifying glass that can look underneath the surface of the object [79]. (d) Image of a textile-fiber reinforced rubber tube with a defect in the center [80]. The dark spots aligned right and left are cross-sections of textile-fibers reinforcing the rubber matrix.

can be built from air coils which produce excellent field homogeneity for spectroscopic analysis. The advantage of electromagnets is the freedom of varying the magnetic field strength. The disadvantage is that measurements are hard to conduct without pre-polarization or alternative schemes of signal detection.

4.3.1. Spectroscopy inside a magnet

A coffee-mug size Halbach magnet for ^1H NMR spectroscopy at 30 MHz has already been built which provides NMR spectra from liquids in conventional 5 mm diameter sample tubes (Fig. 1b) [82]. The performance of such small NMR devices is equivalent to the NMR spectrometers of 30–40 years ago and is well suited for spectroscopy of small molecules. As the magnets are small, self-shielding, and do not require electrical power for operation, they can be densely stacked into arrays for high-throughput operation and employed as sensors in permanent alert mode at a chemical site. Applications of great demand appear to be in combinatorial chemistry, the study of cell cultures [6,7,34,40], and routine analysis of small molecules. The spectroscopic resolution can be improved by further shimming and by reducing the size of the sensitive volume by resorting to capillary sample tubes with micro-coils, with the added benefit of low rf power for excitation [6,7].

NMR spectroscopy at ultra-low fields at this time is of fundamental interest in understanding strong coupling, as the spin interaction energies then compete with the Zeeman interaction energy or even dominate the NMR spectrum. A simple way to boost the sensitivity is to pre-polarize the sample by a magnetic field stronger than the detection field. As the pre-polarization field does not need to be homogeneous, this can be done by rapid variation of the electric current in the B_0 magnet coil or by exposing the sample to the strong magnetic field of a permanent Halbach magnet and then rapidly moving it to the weak electromagnet for detection. Such a simple setup with a Halbach magnet is shown in Fig. 7a. A 0.2 cm³ liquid sample is first pre-polarized at 2 T in the Halbach magnet and then transported into the field of an open-gap electromagnet built from two solenoids without shim coils. The electromagnet produces a static field in the range from 1 to 100 G and is homogeneous to about 1 ppm/cm³.

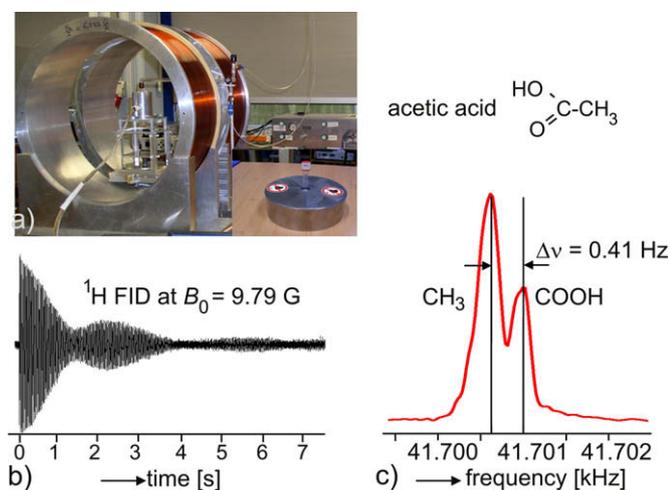


Fig. 7. Spectroscopy with an electromagnet at ultra-low fields. (a) Electromagnet with a diameter of 60 cm for measuring ^1H NMR spectra in the kHz regime and a 2 T Halbach magnet for pre-polarization. (b) Single-scan proton free induction decay of 0.2 ml acetic acid after 90° impulse excitation. Before the signal detection, the sample is magnetized inside the Halbach magnet for a few seconds and then transported into the homogeneous 10^{-3} T field of the electromagnet. (c) The 41.7 kHz ^1H NMR spectrum of acetic acid shows two lines separated by 0.41 Hz which correspond to a chemical shift difference of 9.8 ppm between the COOH and the CH₃ groups.

High-resolution and chemical shift resolved NMR spectra in the kHz regime can readily be measured with this simple setup (Figs. 7 and 9b below). It turns out, that the homogeneity is so good that the ^1H chemical shift can be resolved at 10^{-3} T. This is demonstrated in Fig. 7b with the free induction decay and in Fig. 7c with the single-scan ^1H NMR spectrum of acetic acid. The chemical shift difference of 9.8 ppm between the COOH and the CH₃ groups is well-resolved at the Larmor frequency of 41 kHz. With this setup, the resolution is limited by the magnetic noise in the laboratory. Compared to the shimmed permanent magnets this setup requires somewhat more space, requires sample transfer, and a stable power supply for the electromagnet. On the other hand, the magnet assembly is simple to build, the open design provides access from all sides, the field can be adjusted to detect different nuclear species and chemical shift and spin couplings are all measurable with one setup in different coupling regimes. It is to be expected that such electromagnet will eventually be reduced in size and be shielded to arrive at a simple, mobile, low-field NMR spectrometer for chemical analysis at the site.

4.3.2. Spectroscopy outside a magnet

While for a long time, it was common understanding, that the homogeneous magnetic fields needed to resolve the chemical shift in NMR spectroscopy can only be obtained inside a magnet and not outside, it turns out that shim fields sufficiently strong and accurate to locally homogenize the stray-field can be generated with permanent magnet blocks [43,44]. With such a device, the solution to be analyzed by NMR spectroscopy is contained in a flask on top of the magnet so that the sensitive volume is located within the fluid (Fig. 8a). As the field is homogeneous, the NMR spectrum (Fig. 8b) is measured in the conventional way by simple pulse excitation, with the exception that the excitation pulse is applied in the presence of a pulsed gradient field to selectively excite the spins only in the region where the detection field is homogeneous. This measurement provides proof of principle that NMR spectra can indeed be measured in the stray-field of permanent magnets. Potential applications are envisioned in inline monitoring of chemical reactions by spectroscopic analysis through inspection windows in reactor walls and in discerning fat and water in biological tissue like skin.

Stray-field NMR is, in a way, an old idea, as NMR has been performed in the earth magnetic field for a long time [83–89]. The experimental set-up is similar to the one described above for NMR at ultra-low field inside the magnet, and a convenient way to enhance the signal strength is to pre-polarize the sample [90,91] (Fig. 9a). Without magnetic contamination nearby, the spectroscopic resolution is excellent, as the sample size is vanishingly small compared to the size of the magnet, and ^1H line-widths with a resolution of the order of 10 mHz can be obtained [13,90]. With the exception of Xe [12], the chemical shift is difficult to resolve at such low fields (cf. Fig. 7c), so homonuclear indirect couplings appeared to be inaccessible, and earth-field NMR spectra were believed to be of marginal interest only for chemical analysis in terms of hetero-nuclear couplings [91–95]. However, the magnetic inequivalence of the chemical groups can be lifted by the presence of a magnetic hetero-nucleus such as ^{13}C , enriched in the methyl group of ethyl-alcohol [12–15]. Then the network of homo- and hetero-nuclear J -couplings becomes observable, which produces an abundance of resonances which, when analyzed in the strong-coupling limit prevailing at low field, provides a wealth of chemical information (Fig. 9).

Depending on the field strength and the interaction strengths, different coupling regimes are observed (Fig. 9b and c). In the Earth's field (Fig. 9c and d), the lines are extremely narrow, and long-distance coupling constants can be determined with high precision. Ultra-narrow lines with a width of a few milli-Hertz are

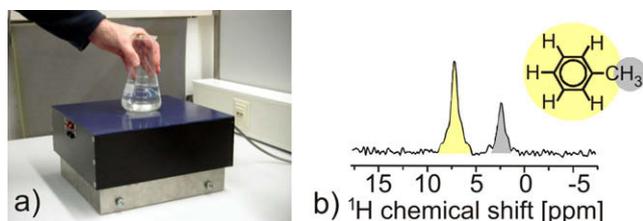


Fig. 8. Stray-field NMR Spectroscopy with a permanent magnet. (a) Stray-field NMR magnet with a homogeneous sensitive volume inside the liquid contained in the flask on top of the magnet. (b) NMR spectrum of toluene contained in the flask [43,44]. The spectroscopic resolution is 0.25 ppm across a sensitive volume of 12 mm^3 .

observed for transitions between spin states with high singlet character [15]. This type of high-resolution stray-field ^1H NMR spectroscopy promises to be of interest for nitrogen-containing molecules such as proteins and peptides, where the abundance of the magnetic nitrogen nucleus is naturally high. Currently, such low-field experiments need to be conducted in the highly homogeneous fields which prevail in areas distant from civilization, where magnetic contaminations are absent. To become a routine tool of chemical analysis, magnets like the one in Fig. 7a with highly homogeneous and low field strengths need to be developed, which are well shielded from outside influence and can be used inside a laboratory.

5. Outlook

Desk-top NMR spectrometers and well-logging NMR devices have been used for relaxometric analysis of a variety of materials and substances for quite some time, but NMR spectroscopy was difficult to conduct with small magnets, as the necessary degree of field homogeneity could not be achieved until recently. Today, advances in shimming permanent magnets have led to the availability of small portable magnets the size of a coffee-mug and smaller, but nevertheless suitable for NMR spectroscopy. When using permanent magnets for shimming, a power supply to maintain shim currents is not needed and such magnets are easy to keep ready for use on demand. Halbach magnets are favorable in that

they are self-shielded, nearly without a stray-field, and the field direction is transverse to the bore of the magnet for convenient use of sensitive solenoidal rf coils. But also open magnets with a sensitive volume external to the magnet can be shimmed for sufficient homogeneity to conduct NMR spectroscopy or for linear field profiles suitable for NMR imaging.

The availability of such small magnets provides vast new opportunities for employing NMR. These are envisioned in three areas. One is high-throughput applications and permanent installations of NMR devices, as the cost of NMR spectrometers with permanent magnets is at least one order of magnitude lower than that of spectrometers with super-conducting magnets [96]. Another is NMR applications where mobility is required to perform the analysis at the site of interest, for example for non-destructive testing of large objects by stray-field NMR, food inspection in department stores and authentication of trade goods. The last one is NMR at extreme conditions, for example, under the chemistry hood, in high pressure laboratories, and other zones of danger.

Yet for NMR devices to become convenience tools, some issues remain to be solved. The temperature drift characteristic of permanent magnets needs to be reduced. This can be solved in different ways, for example, by canceling the drift in the sum of two magnetic fields, by thermal insulation of the magnet, by electronic drift compensation, and by sophisticated NMR measurement schemes such as the shim-pulses that are designed to balance time-dependent drifts and weak field inhomogeneities [97–99].

Another issue is the low sensitivity inherent to NMR in weak magnetic fields. This problem can be addressed from two directions. One is to enhance the nuclear polarization beyond its thermal equilibrium value by hyper-polarization techniques. The other is to boost the sensitivity of signal detection by using super-conducting quantum interference devices [25–29], or the more promising, optical detection [11,30–33] instead of conventional Faraday induction. Different hyper-polarization techniques are known in NMR. The nuclear magnetization of noble gases can be increased by orders of magnitude by spin-exchange optical pumping [16–18], the magnetization of electrons can be transferred to atomic nuclei by dynamic nuclear polarization [19–21], and the anti-phase spin polarization of para-hydrogen can be transferred to other molecules by chemical reaction or via formation of sufficiently long-lived complexes with $p\text{-H}_2$ assisted by suit-

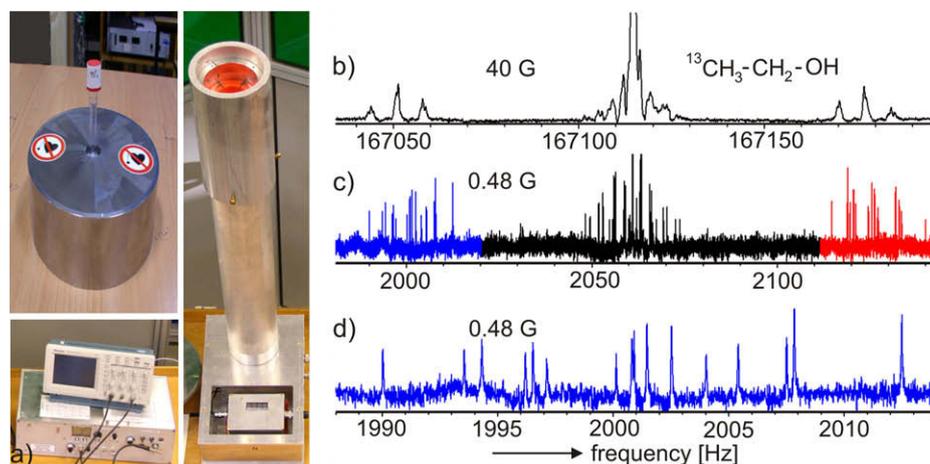


Fig. 9. Earth's field NMR Spectroscopy. (a) Setup for mobile earth-field NMR spectroscopy ($5 \times 10^{-5} \text{ T}$), consisting of a Halbach magnet (top left) to pre-polarize the sample, an rf-shielded NMR probe (right), and the NMR electronics (bottom left). (b) Reference ^1H NMR spectrum of ethyl-alcohol measured with an electromagnet in the intermediate coupling regime at 166 kHz corresponding to $4 \times 10^{-3} \text{ T}$ with site-selective ^{13}C enrichment at the methyl group. The ^1H resonance is split into a pair of three lines corresponding to the triplet of the ^{13}C group and a pair of four lines corresponding to the quartet of the CH_2 group by the indirect homo- and hetero-nuclear couplings. The large central line at 167115 Hz is due to the uncoupled OH-proton. (c) Corresponding single-scan earth-field NMR spectrum [13]. In this strong-coupling regime, the ^1H resonance is split into $56 = 2 \times 16 + 2 \times 12$ highly resolved lines by the indirect homo- and hetero-nuclear couplings. (d) Enhanced view of the left side of (c), showing sixteen resolved lines.

able homogeneous transfer catalysts [23,24]. These are hot topics of current research and it can be expected that for certain classes of molecules and applications, sensitivity will soon be less of an issue.

Last but not least, the human interface of the NMR machines needs to be made more user-friendly. The measurement technology behind most applications of NMR is not more complicated than the technology behind making a call on a cell phone. Yet any child can operate a cell phone, while it still takes intensive training to properly operate NMR spectrometers. Of course, many applications are in science, and even if the NMR output is not a spectrum but a molecular structure, the operation of the NMR spectrometer may be left to a trained scientist. But in a production environment, in materials testing, and in medicine, deviations from a reference are analyzed, which requires less training of the operator. The reference may be a spectrum, relaxation rates, signal amplitudes or any mixture of NMR parameters like the relaxation-weighted spin density w used in depth profiling. This approach is best known from imaging, as deviations from pixel values define image contrast. To identify even small differences between noise-contaminated experimental data, suitable data mining procedures need to be [100–103] developed along with reference data bases for different types of applications. With this beginning to happen, NMR is moving from the specialist's tool of a few to a convenience tool for the many. A growing demand is expected to trigger the development of an NMR operating platform that is not method oriented, but subject or material oriented and intuitive to employ for the untrained user.

While the focus of this discussion was on magnets, it should also be noted, that single-chip spectrometers are being developed to reduce the operating electronics [35,40]. With micro-coil operated spectrometers, bulky rf amplifiers are not necessary, and the entire electronics can be shrunk to sizes much smaller than the portable magnet. To investigate larger samples with low power in homogeneous fields, the strong single rf excitation impulse can be broken down into many [104,105]. If 1000 small impulses are used instead of one strong one, the rf power may be reduced by 6 orders of magnitude, so that even NMR spectrometers for conventional 5 mm diameter sample tubes may eventually be operated with a button cell as the energy source and placed in a small corner of a table or further along, into the pocket of a jacket next to the cell phone [106].

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