Ultralow-Field NMR Spectroscopy

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Magnetic Resonance at or below the Earth's Magnetic Field**

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It is difficult to think of structure elucidation without nuclear magnetic resonance (NMR) spectroscopy or modern diagnostic methods without magnetic resonance imaging (MRI). To achieve higher resolution, chemical-shift dispersion, and sensitivities, the quest continues for (superconducting) magnets that deliver ever-higher magnetic-field strengths with excellent homogeneities. Whether this aspiration is expedient or if one could also do with much lower magnetic-field strengths depends strongly on the kind of application. This Highlight outlines the advantages and challenges as well as the technical realization and application of magnetic resonance (MR, NMR, and MRI) at magnetic fields at or below the strength of the Earth's magnetic field.

If a nucleus with non-zero nuclear spin is introduced into a magnetic field, a splitting occurs of the energy levels of the nucleus, which are degenerate for spin-$^1/_2$ nuclei in the absence of magnetic fields (Zeeman effect). Transitions between these energy levels can be induced and observed, leading to what is known as magnetic resonance. The frequency of these transitions and therefore of the observed resonance phenomena, the Larmor frequency ω_0, depends on the kind of nuclei observed, as quantified by the gyromagnetic ratios γ, and is directly proportional to the size of the energy difference ΔE and hence on the magnetic field B_0 [Eq. (1)].[1,2]

$$\Delta E = \hbar\gamma B_0 \equiv \hbar\omega_0 \quad (1)$$

This leads to the well-known dependence of resonance frequency on the applied magnetic field. Another consequence, however, is the dependence of polarization on the magnetic field as the Zeeman levels are populated according to the Boltzmann distribution.

These two fundamentals of magnetic resonance lead to important consequences both from a technical as well as from an application point of view for NMR/MRI at or below the Earth's magnetic field:

- The important issue concerning sensitivity in magnetic resonance is the difference in population, which decreases significantly when the applied polarization field is lowered.
- When Faraday induction of the observed signal is applied, as is done with conventional spectrometers, it has to be borne in mind that the induced voltage in the detection coil decreases with decreasing resonance frequency, thus leading to decreased sensitivity.
- The size of the scalar coupling J is independent of the magnetic field. The resonance frequency, however, and with it the chemical shift δ, which results from a small change in the resonance frequency by local magnetic fields within the molecule, is dependent on the magnetic field. So, on moving to ultralow magnetic fields, chemical shifts become negligible[3] and scalar couplings dominate the spectra.
- One of the main sources for line broadening in isotropic solutions of spin-$^1/_2$ nuclei (assuming that there are no dynamic/exchange processes) is transverse relaxation as a result of inhomogeneities of the magnetic field. Line broadening does not only reduce the achievable resolution, but also the signal-to-noise ratio (S/N) is affected adversely. Thus, efficient shim systems have been devised to improve the homogeneity of the magnetic field for high-field MR systems. Much less effort is needed to achieve the same or better relative magnetic-field homogeneity for lower magnetic fields. An efficient shielding from sources of parasitic magnetic fields, however, is essential.
- On lowering the magnetic field in imaging applications, artifacts caused by susceptibility differences[4] are largely eliminated and the image contrast caused by differences in longitudinal relaxation time is enhanced (T_1 weighting).

There have been several reviews on NMR and MRI in the Earth's magnetic-field range,[5] and so only the latest developments in this area are covered

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herein. We start by describing ways of improving sensitivity and alternative detection devices. The lack of sensitivity is one of the main drawbacks for MR at low magnetic fields. To improve sensitivity, there are two "screws" that can be adjusted: one is polarization, the other is detection.

The measurement field and polarizing field do not necessarily have to be of the same strength. It was already reported in 1954[6] that a prepolarizing field can be used to change the population differences and by this means improve sensitivity tremendously. This polarizing field is usually approximately 100 times as strong as the measurement field and mostly aligned perpendicular to the measurement field. If this prepolarization field is switched off quickly (as compared to the longitudinal relaxation time), the polarization of the spins persists while detection occurs at the field strength of the (much lower) measurement field and thus with the associated frequency. Much engineering was done, however, to protect the detection system from detrimental effects of the polarizing field. Other ways of polarization, such as optical pumping (for ^{129}Xe[3]) or cross-polarization of nuclei with hyperpolarized gases (e.g. ^{1}H cross-polarized with ^{129}Xe[7]), cryogenic prepolarization,[8] and dynamic nuclear polarization (DNP),[9] have been only seldomly used, if at all, at ultralow fields until now.

Concerning the detection, there are three possibilities currently available. The signal can be detected by Faraday induction as is done in conventional high-field instruments. The induced voltage U_{ind} is proportional to the number of windings n of the coil and the rate of change of the magnetic flux Φ [Eq. (2)].

$$U_{ind} = -n\frac{d\Phi}{dt} \tag{2}$$

The higher the resonance frequency, the faster the rate of flux change and the higher the voltage induced. Thus, sensitivity is considerably reduced at ultralow magnetic fields as a result of the much lower resonance frequencies. Commercial NMR systems that operate at the Earth's magnetic field[10] use this technique together with prepolarization with a polarizing field but usually require samples with volumes of several hundred milliliters. This drawback is usually more than compensated for by the low cost and portability of such systems—as was shown, for example, in the examination of Antarctic sea ice[11]—as no cryogenics are needed. Recently, it was shown by Appelt et al. that it is possible to perform prepolarization in a Halbach magnet, then transfer the sample manually into the probe, which also contained a well-shielded preamplifier, and detect signals with S/N ratios of 3–100 for a single acquisition on 2 cm^3 samples.[12]

There are two other detection methods, namely detection through superconducting quantum interference devices (SQUIDs) and atom magnetometers. Both devices measure the magnetic flux itself and not a change in magnetic flux (as is the case with Faraday induction) and therefore exhibit excellent sensitivity.

SQUIDs are very sensitive detectors of magnetic flux which consist of a superconducting loop interrupted by one (radiofrequency (rf)-SQUID) or two (direct-current (dc)-SQUID) very thin barriers of normally conducting or electrically isolating material.[5b,c,13] The Cooper pairs can tunnel coherently through these barriers, which are called Josephson junctions. For currents below a critical value, the pair tunneling constitutes a supercurrent; for currents greater than this critical value, a voltage appears. The second basis of the mode of operation of SQUIDs is flux quantization: only whole-numbered multiples of the flux quantum Φ_0 (2.07×10^{-15} V s (= T m^2)) can be enclosed in superconducting loops. When an external magnetic field is applied to the closed superconducting loop, a circulating supercurrent is induced that maintains the enclosed flux at its original quantized value. Depending on the mode of operation of the SQUID (rf or dc), either the voltage across the loop changes (dc-SQUID) or the voltage in an inductively coupled tank circuit changes (rf-SQUID). The voltage-flux characteristic is periodic with Φ_0. Usually the response of the SQUID is linearized by operating it in a flux-locked mode, enabling one to both detect minute changes in flux ($\ll \Phi_0$) and track changes in flux much greater than Φ_0. In contrary to the aforementioned Faraday induction, the response of the SQUID to a magnetic field is independent of frequency which makes it an ideal broadband detector for MR. In most applications, magnetic fields are not detected directly but a pickup loop is inductively coupled to the SQUID (see Figure 1).

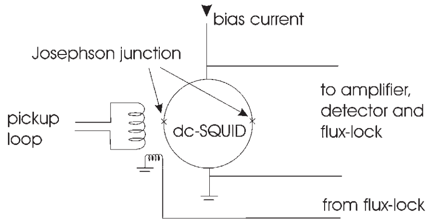

Figure 1. Schematic diagram of a dc-SQUID with pickup loop and flux-lock loop.

Depending on the layout of the pickup loop(s), even suppression of noise from distant noise sources is possible so that when using gradiometer[14] configuration weak signals can be detected against a background of magnetic noise (see Figure 2). This distinction is based on the fact, that nearby (weak) signal sources cause much stronger field gradients than distant (strong) noise sources (e.g. the 50–60 Hz parasitic fields from power supplies).

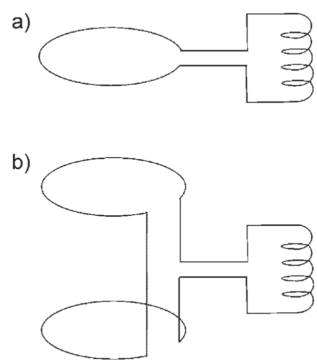

Figure 2. Different layouts for pickup coils: a) The magnetometer layout consisting of a single pickup loop; b) (first-derivative, axial) gradiometer layout with two pickup loops wound in opposite directions.

The excellent sensitivity of SQUIDs is exemplified by their use for the detection of magnetic fields produced by the brain in magnetoencephaly systems (MEG) or by the heart in magnetocardiography systems (MCG).

The obvious advantages of SQUIDs are their extremely high sensitivity (femtotesla (fT) range) combined with frequency independence of signal detection which make them ultimately suitable for MR applications at ultralow fields. Depending on the material the SQUID is made of, namely high-T_c[15] or low-T_c superconductors, cooling of the SQUID with either liquid nitrogen or liquid helium is necessary. The sample is, of course, kept at room temperature—a design challenge on its own.[16] The cryogenics used in these systems are much less expensive than conventional superconducting high-field MR instruments. The ideal system, however, would also be portable, which is impossible as long as cryogenics are used.

Although atom magnetometers have been known since the 1960s,[17] they have been very seldom used for MR detection. The latest developments in atom magnetometer techniques,[18] however, have very recently lead to extremely promising examples of implementation and application in MR detection.[19]

The mode of operation of atom magnetometers relies on the Zeeman effect. A change in the magnetic field leads to a change in the difference of the energy levels and therefore to a change in resonance frequency [cf. Eq. (1)], which can be detected. The most simple device is the proton precession magnetometer, which uses the nuclear Zeeman effect of the hydrogen atom for detection. If, however, not the difference in the nuclear energy levels but in the electron energy levels of alkali atoms (in vapors of these atoms) is used (employing the electron Zeeman effect), optical pumping *and* optical detection can be applied, leading to a much increased sensitivity of this detection device.[17,18] Optical pumping creates an increase in the population of special energy levels of the ground state $n^2S_{1/2}$ of the alkali atoms, thus leading to magnetization in the direction of the pump laser (or the magnetic field that causes the Zeeman effect[20]). If now the magnetic field (resonance) that is to be determined is applied (best: at right angles to the magnetic field that causes theZeeman effect or to the pump laser), the magnetization vector tilts and/or relaxation occurs. There are two ways to quantify the magnetic field: It can be determined through relaxation by examining the optical transmission of the pump beam. After relaxation, atoms need to absorb photons to be pumped into the higher energy level again and so the transmission of the laser beam changes. The second way to detect the magnetic field/resonance is to observe the tilt of the magnetization as a measure of the applied magnetic field. The tilt of the magnetization vector can be read by means of the rotation of the plane of polarization of a second circularly polarized laser (probe laser); the stronger the field, the greater the tilt of magnetization will be, and the more the plane of polarization will be rotated.

With respect to sensitivity, care has to be taken, however, that spin-exchange relaxation (caused by collisions of atoms in the vapor) does not lead to a fast loss of signal. This is achieved in the so-called spin exchange relaxation free magnetometers,[18a] where a sensitivity of $0.5\,\mathrm{fT\,Hz^{-1/2}}$ on a $0.3\,\mathrm{cm^3}$ volume sample was achieved. These above processes, however, need the alkali atoms to be in gaseous form, therefore the magnetometer/vapor cell needs to be maintained at elevated temperatures (180 °C for potassium) and so additional cooling needs to be performed for the measurement at ambient temperature. For example, a water-cooling pad was used to insulate the head of a person during MEG using an atom magnetometer.[19d]

As compared to SQUIDs, atom magnetometers allow for even higher sensitivity as detection is carried out optically. The cost of equipment and maintenance are lower as no cryogenics are needed, which also makes the system in principle portable, but it seems that some engineering challenges still remain to be solved before MR detection with atom magnetometers at low magnetic fields becomes the standard.

It should be mentioned that although NMR and MRI rely on the same general principle, imaging in ultralow magnetic fields is more of a challenge. For imaging, magnetic-field gradients are used to encode spatial information into the NMR frequency. In high-field MRI, these gradients can easily be much smaller than B_0 so that their perpendicular components (called concomitant fields), which lead to poorer image fidelity and resolution, are effectively truncated. This is not the case in ultralow magnetic fields, but these concomitant fields can be averaged using an innovative pulse sequence.[21]

We now turn our attention towards the applications in spectroscopy and imaging, but will forebear from discussing which of the afore mentioned technical schemes were used.

As the chemical shift/resonance frequency is field-dependent, chemical-shift information is lost in ultralow fields,[3,22] whereas J couplings are field-independent and remain observable. This applies, however, only to heteronuclear coupling constants, as spins of the same species appear isochronous and the spectra therefore do not show homonuclear couplings. Depending on the detection bandwidth and the strength of the magnetic field, spins of different species (e.g. ^1H and ^{19}F or ^1H and ^{31}P) can, however, be observed in the same spectrum. Indeed, even two-dimensional ^1H–^{19}F COSY spectra of 2,2,2-trifluoroethanol (see Figure 3) and 1,4-difluorobenzene were achieved at the Earth's magnetic-field strength.[23] The Earth's magnetic field lies in the range of 25–75 μT ($1\,\mathrm{T} = 1\,\mathrm{kg\,s^{-2}\,A^{-1}}$) and gives rise to proton resonance frequencies of approximately 2 kHz. The strength of the Earth's magnetic field depends on the location, and there are daily variations of up to 25 nT.

As the line width is usually much narrower in ultralow fields, the obtainable precision for heteronuclear coupling constants is much higher. So "pure J spectroscopy", as this use of MR at ultralow fields is called, can be used for

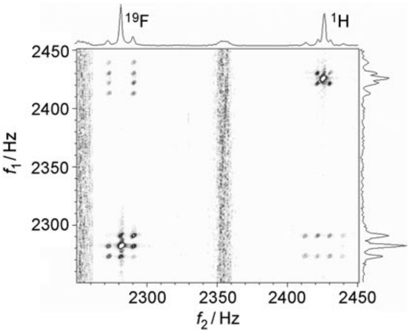

Figure 3. ^1H–^{19}F 2D COSY spectrum of trifluoroethanol. Reprinted from Ref. [23], with permission from Elsevier.

the precise measurement of heteronuclear coupling constants (e.g. ^{1}H–^{29}Si,[12] ^{1}H–^{19}F,[12,24] and ^{1}H–^{31}P[24,25]). If the magnetic field is lowered further (special magnetic shielding is needed to do so) to the nT range, it has been observed that even heteronuclear spin systems (as exemplified for 2,2,2-trifluoroethanol) can become higher-order spin systems.[26,27] Unfortunately, pure J spectroscopy is limited to rather simple or highly symmetric systems, as heteronuclear coupling constants (of different size) for different moieties can be obtained but not assigned without the use of high-field spectra. It can, for example, not be used for the measurement of heteronuclear residual dipolar couplings (RDCs).[28] It was shown that the precise knowledge of heteronuclear coupling constants (as exemplified in Ref. [12] for ^{1}H–^{29}Si coupling constants) is of high analytical potential and can in principle used for online reaction monitoring.[12,24]

There are more arguments for using ultralow fields for MRI than there are for spectroscopy. Apart from being less expensive and less demanding on infrastructure than high-field scanners, MRI at low fields also profits from fewer susceptibility artifacts and a bigger dispersion in T_1 (longitudinal relaxation) times.

When a heterogeneous sample is placed in a magnetic field, the susceptibility differences cause an inhomogeneity in the local magnetic field, leading to a local change in resonance frequency. As the position of an object is encoded through its resonance frequency, images can be severely distorted. Distortions of this kind can be minimized by lowering the measurement field.[29] This would be especially beneficial in medical imaging. Patients with metallic implants could be examined at low magnetic fields, as higher fields are a safety hazard for such patients.[30] Moreover, high magnetic fields render the use of metallic (or not susceptibility-matched) surgical instruments impossible. To exemplify the utility of ultralow-field imaging, images of a bell pepper in an aluminum can were recently recorded at 66 μT, which essentially are identical to those without a can (see Figure 4).[31] Virtually no screening of radiofrequency pulses or signal nor distortion by eddy currents is observed.

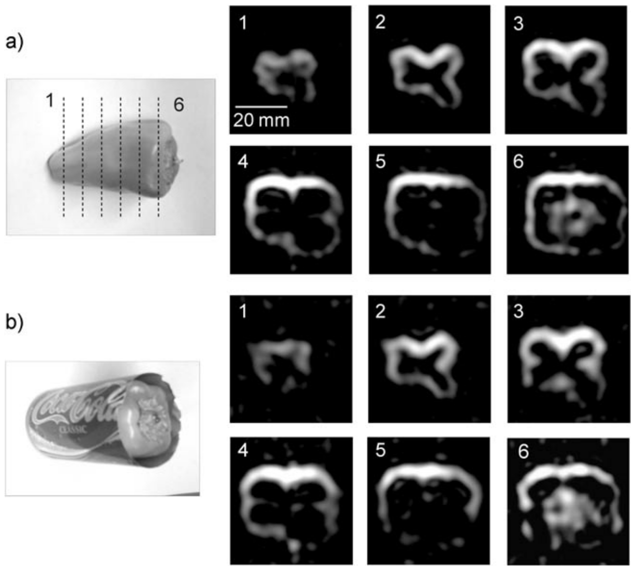

Figure 4. Cross-sectional images (1–6, respectively) of a) a bell pepper and b) a bell pepper enclosed in an aluminum can. Reprinted from Ref. [32], with permission from Elsevier.

Furthermore, it has been shown that it is possible to perform weighting according to T_1 times. As a result of the larger dispersion of T_1 values at low fields, these images have a much higher contrast, which could be beneficial for the imaging of tumors.[31,32] When in vivo imaging is performed, however, it should be noted that transverse relaxation times (T_2) can be rather short so that there can be substantial signal loss. The difference in T_2 times of different tissues leads to what is called T_2 weighting. Areas with short T_2 times (muscle, bones) appear dark in the image, whereas areas with long T_2 times (fatty tissue, yellow bone marrow) appear bright (see Figure 5). One of the advantages of all gradiometers,[33] namely the ability to differentiate near and far magnetic-field sources, can lead to a problem in imaging, as there is a decay of signal along one direction as a result of the increasing distance to the bottom loop of the gradiometer pickup loop (see Figure 5).[34]

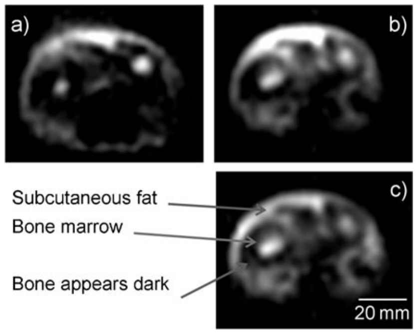

Figure 5. a, b) Two cross-sections at different positions of a forearm. c) Same image as shown in part (b) but with amplitude correction.[34] Copyright 2005, IEEE.

There are even attempts to simultaneously perform MEG and MRI, as the source localization of MEG signals is performed by combining data from MRI at high fields and MEG, measured on two separate systems. It would be extraordinarily useful if both could be performed with the same system and at the same time.[35]

In summary, we have tried to shed some light on the newest technical developments and applications of magnetic resonance at or below the Earth's magnetic-field range by describing the associated problems, namely low sensitivity and low polarization, and the technical ways of addressing them. We described in some detail the well-established (Faraday induction, SQUID) but also very promising new (atom magnetometer) ways of detecting such weak signals. As far as applications are concerned, we highlighted the measurement of heteronuclear coupling constants (pure J spectroscopy) and, in our opinion, the very useful aspects of magnetic resonance imaging at ultralow fields, namely T_1 weighting and suppression of susceptibility artifacts. We are very curious as to when the first systems of this type will make their way into hospitals.

[1] C. P. Slichter, *Principles of Magnetic Resonance*, 3rd ed., Springer, Berlin, **1990**.

[2] The effective magnetic field B_{eff}—the nuclei sense—can be separated into the (usually large) polarizing (and measurement) field B_0 giving rise to the Larmor frequency and the local magnetic field B_{loc}, which results from interactions within the molecule and gives rise to the chemical shift. Inhomogeneities (temporal or spatial) in B_0 also lead to different B_{eff} for the nuclei, leading to slightly different frequencies and in total to line broadening.

[3] This is valid except for ^{129}Xe, for which chemical shifts are extremely sensitive to its environment. For resolution of ^{129}Xe chemical shifts at ultralow fields (ULF), see: a) S. Saxena, A. Wong-Foy, A. J. Moule, J. A. Seeley, R. McDermott, J. Clarke, A. Pines, *J. Am. Chem. Soc.* **2001**, *123*, 8133–8134; b) A. Wong-Foy, S. Saxena, A. J. Moule, H.-M. L. Bitter, J. A. Seeley, R. McDermott, J. Clarke, A. Pines, *J. Magn. Reson.* **2002**, *157*, 235–241; c) S. Appelt, F. W. Häsing, H. Kühn, J. Perlo, B. Blümich, *Phys. Rev. Lett.* **2005**, *94*, 197602.

[4] The magnetization $\overrightarrow{M}$ is defined as $\overrightarrow{M} = \frac{\overrightarrow{B}\chi}{\mu_0}$, where μ_0 is the magnetic permeability constant and χ is the magnetic susceptibility (see Ref. [1]).

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[9] See, for example: N. M. Loening, M. Rosay, V. Weis, R. G. Griffin, *J. Am. Chem. Soc.* **2002**, *124*, 8808–8809.

[10] Such as Terranova from Magritek, Wellington, New Zealand: http://www.magritek.com/terranova.html.

[11] P. T. Callaghan, C. D. Eccles, *Bull. Magn. Reson.* **1996**, *18*, 62–64.

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[14] In a gradiometer, two measurement devices (magnetometers or pickup loops) are arranged in opposite direction so that they report the difference (the "gradient") of the magnetic field.

[15] T_c is the critical temperature below which the material becomes superconducting.

[16] S. Kumar, B. D. Thorson, W. F. Avrin, *J. Magn. Reson. Ser. B* **1995**, *107*, 252–259.

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[26] A spin system is said to be of higher order (strongly coupled) if the splitting that results from coupling is greater than ten times the difference in resonance frequency (chemical shift difference) of the coupling partners. This is observed quite often in homonuclear spin systems of organic compounds (e.g. diastereotopic benzylic protons), but is very unusual for heteronuclear spin systems.

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[33] A SQUID gradiometer is used here, but this is a general problem of gradiometers and also applies to gradiometers based on atomic magnetometers.

[34] M. Mößle, W. R. Myers, S.-K. Lee, N. Kelso, M. Hartridge, A. Pines, J. Clarke, *IEEE Trans. Appl. Supercond.* **2005**, *15*, 757–760.

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