Mobilizing magnetic resonance

Nuclear magnetic resonance traditionally requires large magnets that make the technology immobile and expensive. **Boyd Goodson** describes how efforts are being made to develop portable devices that will extend the reach of this powerful imaging technique

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From iPods to space probes, technological progress is driven by the mantra "smaller, faster and cheaper". Yet for the past few decades one of the best known techniques in physics – nuclear magnetic resonance (NMR) spectroscopy – has followed a different principle: bigger is better. In order to detect the tiny magnetic moments of nuclei, the magnets in state-of-the-art NMR devices can weigh up to several tonnes and cost millions of dollars to build and maintain. This severely restricts applications of NMR because the sample always has to be brought to the machine.

NMR spectroscopy is a vital tool in the physical sciences. It allows chemists to study reactions in exquisite detail, biochemists to probe the dynamics of proteins, and materials scientists to obtain structural information about bulk and nano-scale materials. The best known application of NMR, however, is medical imaging. Since the 1980s magnetic resonance imaging (MRI) has provided a non-invasive way to visualize damage and disease in human tissue without the use of ionizing radiation. And its more recent variant – functional MRI or fMRI – has enabled researchers to map which regions of the brain are involved in certain physical or mental tasks.

Yet for all its advantages, NMR suffers from a number of seemingly inescapable limitations. Its reliance on large magnetic fields, for instance, makes the equipment expensive, difficult to maintain and even potentially dangerous. Moreover, the size of the magnets severely restricts the mobility of NMR. This is in contrast to most other spectroscopic and imaging technologies, which have benefited from miniaturization trends in light sources and detectors to provide low-cost devices that scientists can take into the field.

However, physicists, chemists and engineers are now threatening to turn NMR's fixation with size firmly on its head. By fundamentally changing the way the technique is actually performed, their goal is to make NMR more portable yet more sensitive, and allow the power of the technology to be applied to problems that are currently inaccessible.

At a Glance: Mobile NMR

- Nuclear magnetic resonance (NMR) exploits the spins of nuclei such as hydrogen to provide a spectroscopic tool and a non-invasive medical imaging technique (MRI)
- Traditional NMR devices need large magnets in order to detect the tiny magnet moments of nuclei, which makes the instruments expensive and immobile
- Researchers are developing radical approaches to NMR to make it more portable, enabling scientists to take it into the field and increasing patient access to MRI
- One way to increase NMR mobility is to use weaker magnetic fields or to "borrow" magnetization from neighbouring electrons in the sample
- Other approaches include SQUID detectors, optical magnetometry, force-detected NMR and remote-detection schemes where the nuclear information in a sample is encoded in another substance and transported to the detector via a tube

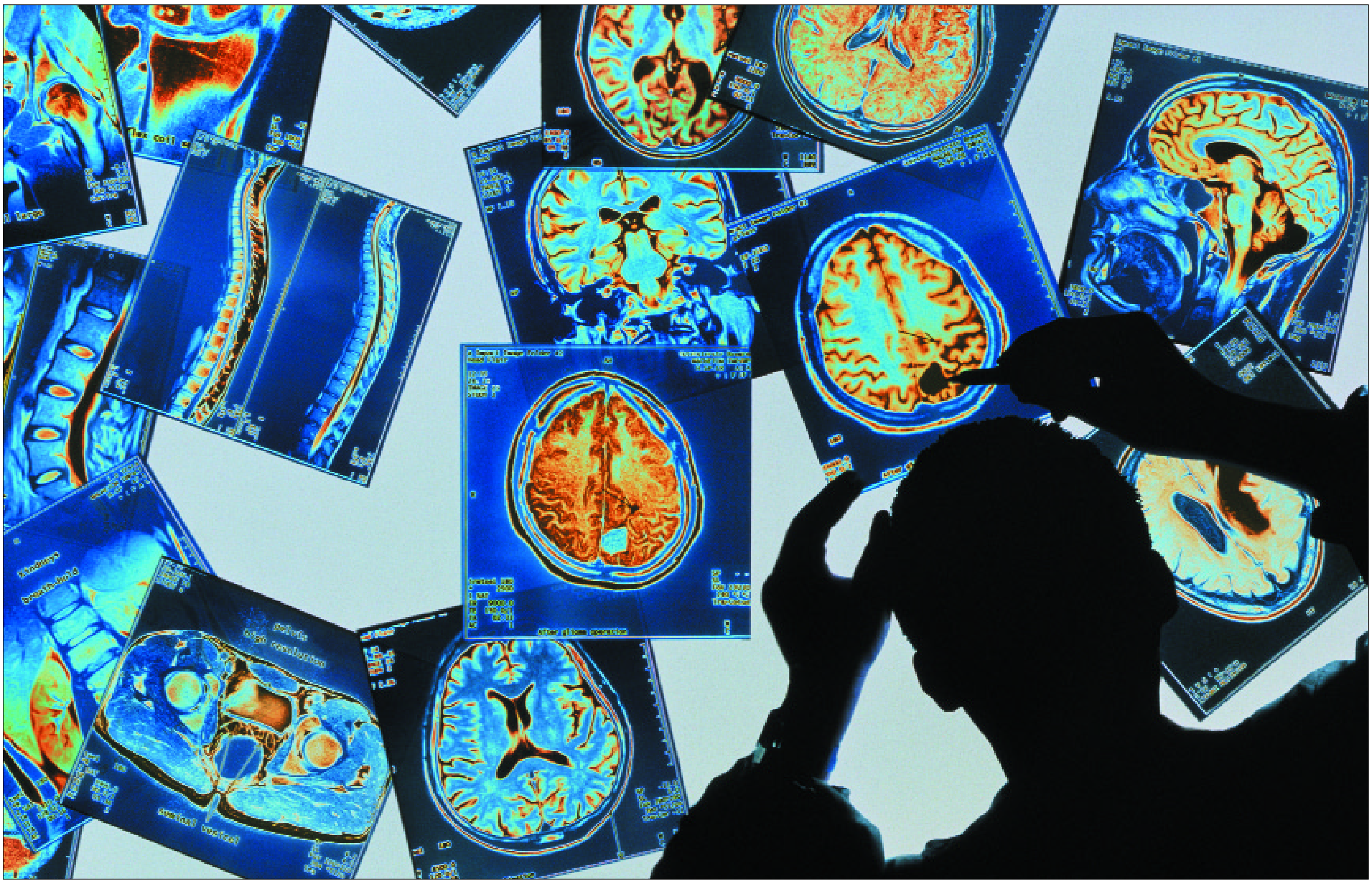
Portable NMR

Nuclear magnetic resonance exploits the intrinsic angular momentum or spin of the nucleus, which causes it to act like a tiny bar magnet. When a sample of material is placed in an external magnetic field, nuclei try to align with the field just like a compass needle points in the direction of the Earth's magnetic field. Quantum uncertainty prevents this alignment from being perfect, so in practice the nuclei precess or wobble around the direction of the field like an off-kilter gyroscope. Crucially, the frequency of this precession or "chemical shift" for a given nucleus is determined by its molecular environment.

The magnetic moments of individual nuclei are too small to be detected individually, which is where the "resonance" aspect of NMR comes into play. By transmitting a radio-frequency (RF) pulse with a certain frequency through the sample via a metal coil, some of the nuclei are driven out of alignment and precess in concert while they attempt to return to their original orientation. Together, these nuclei create a bulk magnetization that induces an oscillating electrical current in the coil. Any nucleus that possesses spin can provide such an NMR signal, although the most commonly measured are hydrogen nuclei due to their prevalence in water and organic substances.

It is the exceedingly weak magnetic field strength associated with nuclear spins that makes NMR devices so bulky. A bigger magnet improves the signal enormously, and allows the technique to distinguish the resonances of different nuclei via their chemical shift. However, the magnets also need to be of exceedingly high quality to ensure that the field strength is constant to within a few parts per billion across the sample – a feat that can only be achieved with large superconducting magnets cooled to a few degrees above absolute zero. These limitations have led to growing efforts to develop alternative ways of performing NMR and MRI, with increasing degrees of success.

One key step towards portable NMR is the NMR "mouse" developed by Bernhard Blümich and co-workers at Aachen University of Technology in Germany in the late 1990s. Principally comprising small permanent magnets a few centimetres across to produce a field of about 0.1 T and a nearly flat wire RF coil, the mouse allows rudimentary NMR analyses to be performed simply by holding the device over the surface of a sample. This is in contrast to conventional NMR or MRI scanners, in which the sample or patient



Geoff Tompkinson/Science Photo Library

Portability in mind
MRI could one day be taken to the patient, rather than the other way round.

is placed inside the centre of a large cylindrical magnet where the field is strongest and of the highest quality. However, the gross non-uniformity of the magnetic fields produced by the mouse blurs the NMR signals from different species and locations within the sample, causing them to appear together as a single broad peak in the spectrum (figure 1).

Last year, the Aachen team joined forces with Alex Pines, Jeff Reimer and co-workers at the University of California in Berkeley to get round this problem. Similar in principle to the NMR mouse, the Aachen–Berkeley device consists of permanent neodymium–iron–boron magnets with a precisely shaped coil centred between them (figure 2). As with conventional NMR, the coil is used both to generate the resonant RF pulses needed to knock the nuclear spins out of equilibrium as well as to detect their NMR response. Here, however, the coil is specifically designed to create spatially non-uniform RF pulses that match the misshapen magnetic field in the sample region. By carefully controlling the timing of the pulses, the non-uniform RF field can be made to cancel out most of the spectral broadening caused by the permanent magnets – refocusing the wayward motions of nuclear spins in different parts of the sample.

Weighing almost 27 kg and with a footprint of $26\times28\,\text{cm}^2$, the Aachen–Berkeley prototype has been likened to an "NMR rat" – and a big one at that! Moreover, the magnetic device has to be connected via cables to a larger spectrometer console that houses the RF circuitry, amplifiers and data-processing computers. Nevertheless, the prototype is orders of magnitude smaller, cheaper and simpler than conventional NMR magnets, and further work could soon allow the entire package to fit within a suitcase. The challenge now is to improve the spectral resolution. While the proof-of-principle device was able to discriminate between fluorine resonances of different fluorinated organic molecules, identifying the ubiquitous hydrogen nuclide requires a 10-fold improvement in spectral resolution.

NMR without the magnet

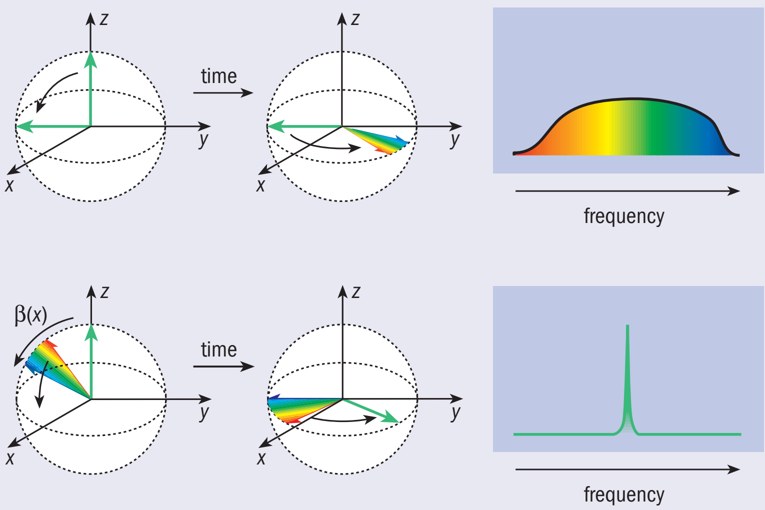
The magnets in the "mouse approach" to mobilizing NMR are weak compared with those in conventional devices, but they are still orders of magnitude stronger than the Earth's magnetic field (which is about $50\,\mu$T). Is there therefore some way of reducing the field to an extreme limit where the NMR magnet is removed entirely while still generating sufficient nuclear magnetization to yield a detectable signal? A number of techniques have recently been developed to solve this seemingly paradoxical problem.

One approach is to "pre-magnetize" the nuclei by first exposing the sample to a strong permanent magnet and then quickly moving it to a simple NMR detector with a low magnetic field. While the nuclear magnetization generated in this way is rather small, it greatly exceeds the negligible values typically obtained in the Earth's field. Just before this article went to press, however, Stephan Appelt, Blümich and co-workers at Aachen demonstrated that such an approach can exploit the ultrahigh spatial uniformity of the Earth's magnetic field to obtain relatively weak but exceptionally high-resolution spectra from different solutions using simple portable devices.

It is the exceedingly weak magnetic moments of nuclei that makes NMR devices so bulky

Another way to perform NMR without the magnet

1 *Ex situ* NMR spectroscopy



NMR spectroscopy can be used to identify the chemical composition of a sample by detecting the way the magnetic moments or spins of certain nuclei precess in the presence of a magnetic field. The stronger and more uniform the field, the more accurate the identification. In a highly non-uniform magnetic field (assumed to be parallel to the *z*-axis), such as those produced by some portable NMR "mouse" devices, spins in different regions of the sample precess at different frequencies once the nuclear magnetization has been "tipped" into the *x*–*y* plane by an RF pulse (top). The detectable magnetization (represented as rotating vectors coloured red to violet to imply slow and fast extremes of precession frequency) therefore spreads out too rapidly and yields broad, featureless spectra. In the Berkeley–Aachen *ex situ* approach, however, the magnetization is tipped away from the *z*-axis into the *x*–*y* plane using similarly non-uniform RF fields. By applying repeated pulses at different times and with different "tipping angles" (β), the magnetization is refocused to provide much narrower spectral lines.

is to generate much higher nuclear magnetization by "borrowing" from the magnetic moments of neighbouring electrons in the sample, which are some 1000 times greater than those of nuclei. Indeed, this approach has been used for many years to enhance the sensitivity of NMR. It typically works best at high magnetic field strengths and at ultralow temperatures, where electron spin magnetization can be generated and subsequently transferred to nuclei most efficiently.

Recently, a related approach called hyperpolarization has been developed. Here, a laser is used to generate high levels of non-equilibrium electron polarization that can be shared with nuclei, enhancing NMR signals by up to five orders of magnitude. Unfortunately, hyperpolarization is only directly applicable to a highly select group of substances, which includes certain semiconductor materials and NMR-active noble gases such as helium-3 and xenon-129. Hyperpolarized gases have generated of a lot of excitement in terms of their potential for low-field NMR applications, particularly since they are chemically inert and biologically safe.

Genevieve Tastevin and co-workers at Ecole Normale Supérieure Paris have recently used hyperpolarized helium to obtain high-resolution images of human lungs in a moderate field of 0.1 T, and were able to perform preliminary spectroscopic measurements in fields of just 3 mT. Last year, however, Ross Mair and co-workers at the Harvard-Smithsonian Center for Astrophysics and the University of New Hampshire used hyperpolarized helium to image lungs using fields as low as 3.8 mT. Their "home built" MRI system employs two pairs of large electromagnetic coils to generate a variable magnetic field of 3–7 mT. Once positioned within the centre of the device, the patient inhales hyperpolarized helium gas via a tube and the helium NMR signals are then detected conventionally using a pick-up coil that resembles a small barrel placed around the patient's chest.

At over 2 m high and surrounded by steel plates to shield the apparatus from RF interference, the imager is hardly a tabletop device (figure 3). Nevertheless, it is a marked improvement over conventional high-field MRI systems, and could bring NMR to those in remote geographical locations. Its open-access design also allows patients to be imaged at different orientations, and opens up MRI to people who suffer from certain acute illnesses or claustrophobia, and to those who have implants.

SQUID-detected NMR

The pre-magnetization and hyperpolarization routes to making NMR smaller and more mobile work by enhancing the strength of the signal sources in low magnetic fields. But another approach to low-field NMR is to alter the way the signals are detected, in particular using superconducting quantum interference devices or SQUIDs. These small electrical components consist of a loop of superconducting material interrupted by two small insulating breaks called Josephson junctions. The way electrons tunnel through the junctions depends on the strength of the magnetic flux passing through the loop, so the slightest change in the flux – created, for instance, by the NMR response from a nearby sample – causes a measurable variation in the current flowing through the loop.

Because SQUIDs measure magnetic flux directly, their sensitivity is independent of the frequency of the signal. This makes them ideal for detecting weak NMR signals at ultralow magnetic fields. The downside is that SQUIDs must be cooled to cryogenic temperatures in order for their superconducting properties to come into play, which limits potential NMR applications as the samples must be cooled as well. Recently, however, a number of research groups have developed insulated SQUID-based detectors that allow samples to be studied in low field but ambient conditions.

For example, in 2002 physicist John Clarke, Pines and co-workers at Berkeley used hyperpolarized xenon gas to enhance the MRI signal from a highly porous aerogel sample in a field of 2.3 mT using a SQUID built from high-temperature superconducting materials. And in 2004 the Berkeley team used a thermally isolated SQUID based on conventional superconductors to image the water distribution in a pepper, demonstrating its potential for ultralow-field MRI. Independently, Michelle Espy and co-workers at the Los Alamos National Laboratory have recently used SQUIDs to perform microtesla NMR on the human brain while detecting other types of magnetic signals – an achievement that could enable brain tissue and neuronal activity to be imaged simultaneously with high resolution.

Physicist Michael Romalis and co-workers at Princeton University have recently used SQUIDs to greatly enhance the NMR signals from liquids in microtesla fields. The researchers first prepared liquid hyperpolarized xenon and then mixed it with common organic solvents such as methanol. Because the xenon nuclear spins are so highly polarized, their mere presence in the liquid mixture forces the hydrogen spins in the organic molecules to deviate from equilibrium. This transfer of magnetization produced NMR spectra a million times brighter than those obtained without the xenon magnetization source. Moreover, this sensitivity will improve considerably with the availability of more-sensitive SQUIDs and better xenon hyperpolarization.

The downside of SQUID-based NMR is that it is very sensitive to RF interference, which means the apparatus needs to be surrounded by bulky electromagnetic shields. Nevertheless, the extraordinarily narrow spectral lines obtained by performing NMR and MRI in such low fields are highly encouraging for the development of portable, low-cost NMR devices. Furthermore, the low-frequency fields involved in the manipulation and detection of the nuclear spins can penetrate more easily into metallic or ionic substances. This property allows NMR signals to be obtained from samples inside metal containers, with possible applications in food science and airport security screening.

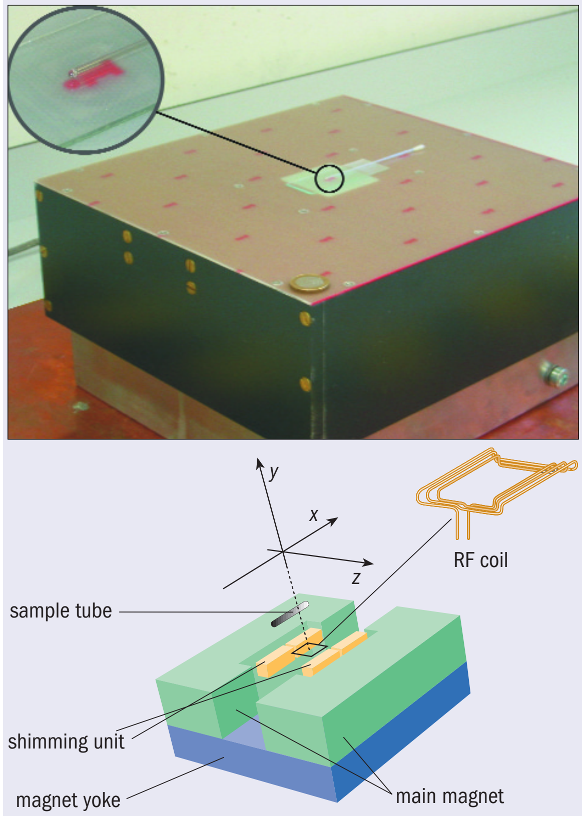
Optical magnetometry

Alternative low-field approaches for detecting NMR signals are not just limited to SQUIDs. Over 30 years ago Cohen-Tannoudji and co-workers at the Ecole Normale Supérieure in Paris showed that the tiny magnetic fields generated by nuclear spins could be detected by probing the interactions of a nearby atomic vapour with light – an approach known as optical magnetometry. While other optically detected NMR schemes have been developed since then, recent technical advances have made optical magnetometry a hot topic once again.

An optical magnetometer closely resembles the set-up used to generate hyperpolarized gases. Atoms of an alkali-metal vapour are first "sensitized" by a laser, which aligns the unpaired electron spins. This allows the electrons to act as a sensor because their spins precess in lock-step in the presence of even the weakest magnetic fields. The precession is recorded by a laser directed though the vapour in the perpendicular direction. In 2004 physicist Dmitry Budker, Pines and co-workers at Berkeley used a rubidium-vapour magnetometer to measure the NMR signal from a sample of hyperpolarized xenon at ultralow fields. And Romalis and co-workers have even used a potassium-vapour magnetometer to detect NMR from pre-polarized water – demonstrating the applicability of the technique to biomedical MRI.

While a number of other engineering challenges have to be resolved before the dream of practical, low-field optical-MRI can be realized, optical magnetometers do offer a number of tantalizing advantages. As with SQUID magnetometers, no inductive coil is used to detect the NMR signal, allowing the magnetic response of the nuclei to be detected directly. Importantly, however, the components of an optical magnetometer could be more easily shrunk to provide a cheap, compact and portable device – especially since they do not require expensive and cumbersome cryogenic technology.

2 Portable NMR device



B Blümich

V Demas

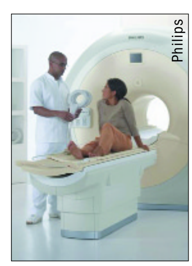
The Aachen–Berkeley portable high-resolution NMR instrument, with a €1 coin placed on its surface to give a sense of scale (top). The inset highlights the sample region. This device, which consists of a series of permanent magnets and a radio-frequency coil (bottom), can be used for rudimentary NMR analyses in the field.

Force-detected NMR

Novel NMR detection schemes such as SQUIDs and optical magnetometry clearly offer great benefits for studies in weak magnetic fields. But what about alternative NMR detection schemes in intermediate fields – in other words, fields that are weak enough to permit high portability yet strong enough to access at least some of the important chemical-shift information? At these higher fields, so-called force-detected NMR methods should be more sensitive than traditional magnetic-induction techniques.

Force-detected NMR measures the mechanical motion of a small device due to the collective forces exerted by the nuclear spins in a sample. One well-known variant of this is magnetic resonance force microscopy (MRFM), in which a micron-scale magnet attached to a tiny cantilever senses the bulk magnetization of nuclei induced by an RF pulse. This alters the motion of the cantilever, which is carefully monitored using a laser to provide the NMR signal.

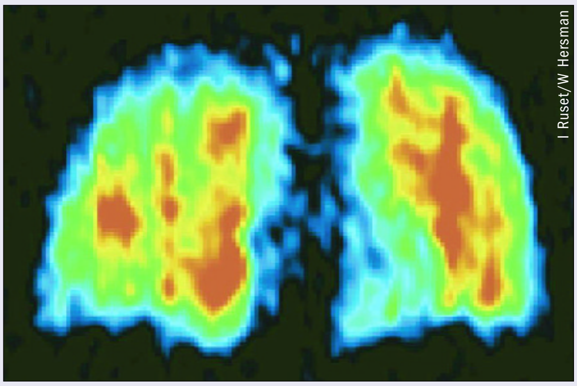
Over the last few years Dan Rugar and co-workers at IBM Almaden in the US have worked tirelessly to improve the sensitivity of MRFM technology, culminating with the detection of single electron spins in 2004 (see *Physics World* October 2004 pp20–21). However, while the greater magnetism of electrons makes them far easier to detect, it is the nuclear-spin response that is of greater interest since it contains more information

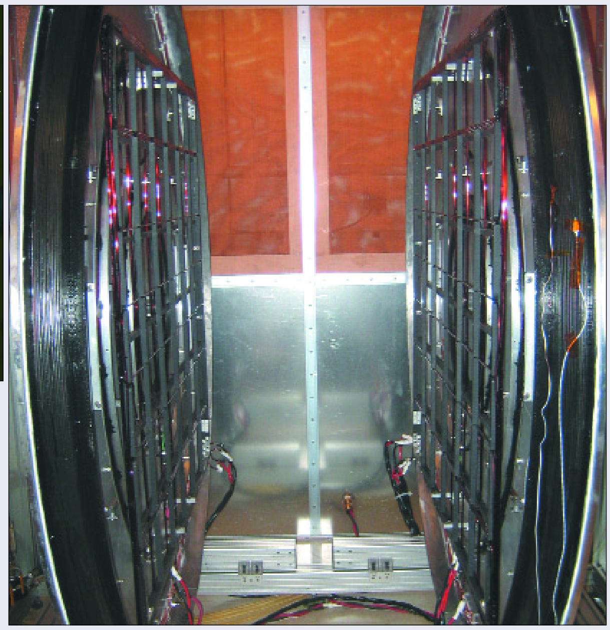


Philips

Big deal
NMR allows the body to be imaged non-invasively, but it does not come cheap.

3 MRI without the magnet





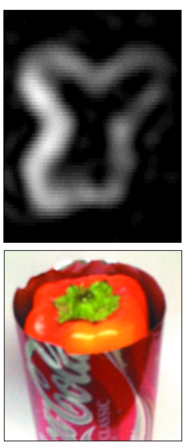
One way to increase the access of NMR and make it more portable is to get rid of the magnet entirely and instead "borrow" magnetism from neighbouring electrons in the sample. Researchers at the University of New Hampshire and the Harvard-Smithsonian Center for Astrophysics have recently used hyperpolarized helium-3 to image human lungs in a magnetic field of 3.8 mT (above). The photograph on the right is a walk-in perspective of the second-generation low-field MRI device built by Harvard-Smithsonian researchers, showing the circular coils and grids used to generate the images.

about molecular structure.

Rugar's group and, independently, John Marohn and co-workers at Cornell University have recently used MRFM to detect NMR signals from sample regions containing less than a billion nuclear spins (conventional NMR typically requires more than about 10^{17} nuclei). This represents an enormous enhancement in detection sensitivity, but the "holy grail" of force-detected NMR is to push this sensitivity down to the single-spin limit – an achievement that might one day allow a single biomolecule to be probed while it performs its duties within a living cell.

The primary goal of MRFM is therefore sensitivity, rather than portability. However, in the late 1990s Daniel Weitekamp and co-workers at Caltech devised an alternative force-detected approach that could lead to portable NMR instruments. The technique – which is dubbed BOOMERANG for "better observation of magnetization, enhanced resolution and no gradient" – uses a device similar in size to the NMR mouse and consists of carefully arranged permanent magnets that generate a strong field. As with MRFM devices, however, the resulting NMR signal is measured not by the coil but via the force that the spins exert on detector magnets located near the sample. The displacements of the oscillating magnets are then monitored and recorded via fibre-optic cable.

In 2004 the Caltech team used BOOMERANG to obtain high-resolution spectra of liquids at room temperature, claiming a 50-fold improvement in detection sensitivity over commercial low-temperature SQUID detectors. Designed with portability in mind, the device is relatively simple and the entire magnetic assembly fits within a bell jar; further miniaturization is under way. Madsen and co-workers envisage a number of field applications for their device, including surface studies of small particles, non-invasive investigations of living cells and robotic explorations of harsh environments.



SQUID-based MRI
A microtesla MRI image obtained from a pepper placed within a drinks can, showing the ability of ultralow-frequency MRI signals to penetrate through metallic walls.

Remote detection

As conventional NMR devices are inherently immobile, samples or patients must always be brought to the magnets. To increase the mobility of NMR, the approaches we have seen so far aim to reverse this equation so that the spectrometer can be moved to the sample. However, one can envisage a totally different approach: one where the sample and spectrometer remain in separate locations and only the *information* about the sample is moved from place to place.

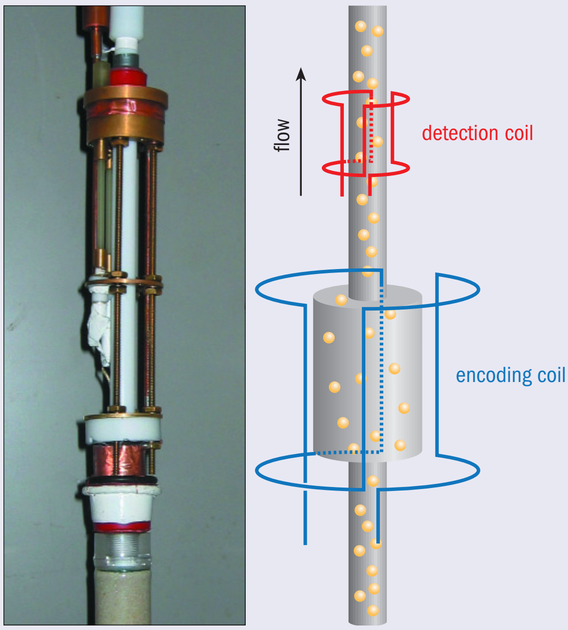
Such remote-detection schemes are already widely developed in optics, such as using lasers to measure air pollution over large distances. However, the low detection sensitivity of NMR makes it ill-suited to such applications, which is why conventional NMR and MRI rely on a single device. This "one size fits all" approach not only contributes to NMR's immobility, it also results in machine designs that may be sufficient for all needs but optimized for none.

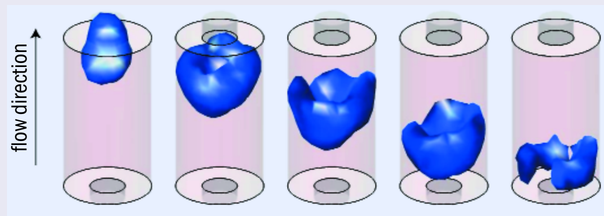
Researchers at Berkeley are devising ways to perform the sensitization, encoding and detection steps of NMR in distinct stages separated in both space and time. This "NMR from afar" approach begins as in conventional NMR, with a sample surrounded by an RF coil. The detection coil, however, resides in a high-field magnet located several metres away connected to the sample environment by flexible Teflon tubing. A probe fluid containing "sensor nuclei" is passed through the sample, where it is encoded with information about the sample's morphology or chemical make-up. The fluid then carries this magnetic information along the tubing into the detection coil where it is recorded (figure 4).

As the sample's information is encoded onto the bulk magnetization of the nuclear spins in the fluid and not, say, their precession frequencies, irregularities in the flow do not distort the signal. Indeed, the only real requirements for the fluid is that it provides a sufficiently strong signal and reaches the detection coil before its nuclear spins have time to return to equilib-

4 Magnetic memory

A Pines





In the new remotely detected NMR scheme being developed by researchers at Berkeley, information about the structure or composition of a sample is encoded onto the nuclei of another substance acting as a sensor fluid. This magnetic information is then transported to the detector via tubing. Here, a sample of porous rock (shaded cylinder in schematic left) is placed in the active volume of the encoding coil. Spatially dependent information is encoded onto the nuclear magnetization of the flowing sensor fluid (hyperpolarized xenon, yellow spheres) and measured as a function of time as different portions of the fluid reach the detector coil. Corresponding information about the structure of the porous sample can be obtained by observing how the sensor fluid travels through different regions of the sample in a so-called time-of-flight NMR experiment (above), in which the time it takes for a given portion of the sensor fluid to reach the detector is compared with the location where the sensor fluid originated within the sample.

We can expect a variety of NMR approaches that have yet to be envisioned, much less attempted

rium. In principle any such fluid could be used, but the clear favourite is gaseous xenon-129. Once hyperpolarized with a laser, this gas provides an extremely strong NMR signal that can last for at least half an hour. Its well known "stickiness" on the molecular level allows it to interact with and probe various molecules and materials surfaces, yet its chemical inertness prevents it from damaging the samples under study.

Recently a collaboration between the Pines group and researchers Pabitra Sen and Yi-Qiao Song from the oil exploration company Schlumberger-Doll used this technique to remotely image fluid flow through porous rock. Such a remote-detection scheme may eventually allow the 3D pore structure of rock to be probed via a bore hole to gauge the prospects for oil recovery. And towards the end of last year, the Berkeley group used the remote-detection approach to enhance the sensitivity of NMR studies involving microfluidics – an emerging field of great importance for bioanalytical chemistry and chemical engineering.

Unlike optical remote-detection methods, the remoteness of the sample in the NMR approach is limited by the ability of the probe fluid to transport the information correctly and efficiently from the sample to the detector. Nevertheless, it is important to realize that the encoding and detection stages need not be particularly distant in order to reap significant rewards. Indeed, one of the biggest potential pay-offs of remote detection is that the instrumentation geometries and the experimental conditions for encoding and detection can be independently optimized.

A miniature future

The unique advantages of conventional high-field systems mean that most NMR applications are in little danger of being supplanted by portable or remote-detection devices, particularly in the case of high-resolution studies of large biomolecules. Nevertheless, in a number of situations where transporting the sample to an NMR laboratory is impractical, unduly expensive or impossible, the on-site availability of high-resolution NMR could be extremely useful. Several such applications can be easily envisioned, including medical diagnoses in doctors' surgeries, inspections at airports and border-crossings, analyses at archaeological digs, the exploration of energy sources, and ultimately even the exploration of planets and other bodies in our solar system.

While the enormous promise of these approaches has already been demonstrated, many are still very much in their infancy; and we can expect a variety of potential applications and approaches that have yet to be envisioned, much less attempted or realized. In the mean time, with continuing advances in NMR portability, sensitivity and device automation the day may arrive where instead of going to a hospital to get an MRI, the MRI will come and get *you*.

More about: Mobile NMR

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