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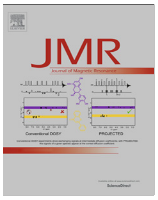

Editorial

High magnetic field science and its application in the United States: A magnetic resonance perspective

Foreword

High-field magnets have become an important research tool in many scientific disciplines. Originally developed for studying the characteristics of materials under extreme conditions, they have increasingly been used by other disciplines, including biology, chemistry, and geology, and have found applications beyond basic science, serving many applied fields from medicine to the petroleum industry. At the request of the United States National Science Foundation and of the Department of Energy's Basic Energy Sciences office, the U.S. National Research Council (NRC) established a committee in the spring of 2012 called the "Committee to Assess the Current Status and Future Direction of High Magnetic Field Science in the United States". This group of Academy-level experts was asked to assess the needs of the U.S. research community in particular – and of the global research community in general – for high magnetic fields. This "MagSci" Committee was chaired by Prof. Bertrand I Halperin, and its mandate included to determine the status and identify trends in the use of high magnetic fields throughout science and technology. Based on its assessment, this group of experts was asked to provide guidance for the future of magnetic field research and technology development in the United States, taking into account worldwide capabilities and any potential for international collaborations and/or cooperative arrangements. The full text of this Committee's report, which was officially released in the fall of 2013,[1] can be found in http://sites.nationalacademies.org/BPA/BPA_067287; this site indicates the full roster of Committee participants, as well as the depositions that were made at the US National Academy of Sciences in support of their activities. Given the exciting new propositions and vistas that arose from this MagSci Committee in general, and their potential implications for the future of all aspects of magnetic resonance (MR) in particular, I decided to request the permission of the NRC to abstract what I consider to be the most MR-relevant part of this report. This summary is presented in the present editorial article, taken nearly verbatim from the original MagSci report. In its preparation it is also a pleasure to acknowledge the assistance of Dr. James Lancaster, Director of the National Academy's Board on Physics and Astronomy; as well as of the MR-oriented members of the MagSci board Profs. Thomas Budinger, John Gore, Ann McDermott, and in particular to our JMR colleague Dr. Robert Tycko.

1. High magnetic fields in chemistry, biochemistry, and biology

High-field cutting-edge magnets play central roles in chemical, biochemical and biological research, primarily through the techniques of nuclear magnetic resonance (NMR) and electron paramagnetic resonance (EPR). In medical research and clinical medicine, high-field magnets are essential components of magnetic resonance imaging (MRI) systems, which create three-dimensional images of anatomical and diagnostic importance from NMR signals. (MRI is described in a separate section below). In all of these techniques, current magnetic field strengths are somewhat below the level that is achieved in specialized high-field facilities devoted primarily to physics and materials research. The magnets are usually produced by commercial vendors, rather than by research teams. Despite the commercial context of their construction, the magnets used for very high field NMR and other spectroscopies present ambitious design challenges: the magnets have exceptionally high homogeneity (∼1 ppb) over large volumes (>1 cm^3 homogeneous volume), requiring highly specialized and sophisticated engineering to manage the concomitant structural stresses and stored energies. The magnets must also have exceptionally high stability for indefinite time periods (months to years), implying that they are typically constructed from persistent superconducting materials. Field strengths in NMR magnets are limited by the properties of these materials, making high-field NMR one of the important scientific drivers for the continuing development of advanced superconducting materials and magnet technology.

2. Importance of high fields in NMR

Higher magnetic fields lead to better NMR data for two main reasons. The first is spectral resolution: The NMR frequency of the nucleus of a particular atom in a molecule or material is proportional to the strength of the external field, but is also affected by the atom's local chemical and structural environment. As the external field increases, differences between NMR frequencies of different atoms become proportionally larger and easier to measure. One of the most important advances in modern NMR methodology, beginning in the mid-1970s, is the development of "multidimensional" NMR spectroscopy, in which NMR frequencies detected in multiple time periods within a single RF pulse sequence are correlated with one another. In an *N*-dimensional NMR spectrum, the effect of increasing magnetic field on spectral resolution occurs in each dimension, so that the number of distinct NMR frequencies that can be measured (which determines the size and complexity of molecules and materials that can be studied by

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[1] National Research Council. *High Magnetic Field Science and Its Application in the United States: Current Status and Future Directions*. Washington, DC: The National Academies Press, 2013.

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NMR) can increase as roughly the *N*th power of the field strength (BN). In practice, in a 3D NMR spectrum of a biological macromolecule such as a protein in aqueous solution in a field of approximately 20 T, NMR signals from more than 10,000 ^{1}H, ^{13}C, and ^{15}N nuclei can be resolved from one another and measured accurately.

The second main reason why higher fields lead to better NMR data is sensitivity: In available magnets, NMR frequencies typically lie in the 100–1000 MHz range, corresponding to photon energies of 4×10^{-7} to 4×10^{-6} eV (5–50 mK). These low energies imply that the degree of nuclear alignment induced by the magnetic field (i.e., the fractional difference between nuclear spin momenta parallel and antiparallel to the field direction, called the nuclear spin polarization) is typically only 10^{-6}–10^{-5} at ambient temperature and is proportional to the field strength. NMR signal amplitudes are proportional to the nuclear spin polarization. Because NMR signals are detected inductively, the signal amplitudes are also proportional to NMR frequencies themselves. Thus, signal-to-noise ratios in NMR spectra can be proportional to B^2. Additional factors affecting sensitivity include the temperatures of samples and electronics, the NMR linewidths, and the repetition rates of measurements (which are limited by spin lattice relaxation rates, the rates at which nuclei align with the magnetic field before each measurement). In practice, an approximately linear dependence of NMR sensitivity on magnetic field strength is often observed. This produces an approximately linear decrease in sample quantities required for NMR measurements, an important consideration especially for biological samples that are difficult to obtain in large quantities.

Two distinct classes of NMR techniques are important in studies of chemical, biochemical, and biological systems. In each class, higher fields produce additional advantages for distinct reasons. The most common techniques, called "solution NMR", apply to molecules that are dissolved in an isotropic liquid (e.g., aqueous buffers or organic solvents). Rapid translational and rotational diffusion in an isotropic liquid make all molecules in the sample structurally equivalent on the nanosecond-to 6 μs timescale. Rapid rotational diffusion also averages out anisotropic nuclear spin interactions, resulting in exceptionally narrow NMR lines and high spectral resolution. However, when molecules become very large, as in the case of high-molecular-weight proteins and nucleic acids, rotational diffusion becomes too slow, resulting in greater line widths that impair both resolution and sensitivity (because the NMR line widths limit the efficiency of nuclear spin polarization transfers that are essential for multidimensional spectroscopy). However, in certain cases, higher fields reduce the NMR line widths of high-molecular-weight proteins and nucleic acids, through a partial cancellation between line width contributions from anisotropic magnetic dipole–dipole interactions, which are independent of field, and anisotropic chemical shielding interactions, which increase linearly with field. Thus, in the case of biologically important macromolecules in solution, higher fields enable multidimensional NMR measurements on high-molecular-weight systems that would otherwise be impossible. Very high fields can also produce a weak magnetic alignment of dissolved molecules, due to anisotropy in their magnetic susceptibility, which leads to incomplete averaging of dipole–dipole interactions among nuclei. Solution NMR measurements of these residual dipole–dipole interactions provide useful constraints on molecular structures, as has been demonstrated for proteins.

The second class of NMR techniques, called "solid state NMR", apply to *bona fide* solids, either crystalline or non-crystalline, that are of interest in materials science, organic and inorganic chemistry, as well as to solid-like biochemical and biological systems, including protein filaments and membrane associated systems. The absence of isotropic translational and rotational diffusion (and, particularly at low temperatures, the absence of internal molecular motions) in a solid typically results in significantly greater NMR line widths and poor spectral resolution. However, the technique of magic-angle spinning (MAS), first demonstrated in the late 1950s and improved dramatically in recent years, in which solid samples are rotated very rapidly about an axis at the "magic angle" $\theta_M = \cos^{-1}(1/\sqrt{3})$ to the magnetic field direction using a pneumatic turbine system, approximates the effects of rotational diffusion, producing solid state NMR line widths that can approach the line widths in solution NMR spectra. Some of the most exciting applications of solid state NMR are possible only at very high magnetic fields. In solid state NMR of organic and biological systems, strong dipole–dipole interactions among ^{1}H nuclei limit the achievable ^{1}H NMR line widths, even under rapid MAS. Therefore, it is only at the highest available fields that ^{1}H NMR spectra of complex organic and biological systems become useful. Inorganic systems of practical and chemical interest (e.g., catalysts, glasses, battery materials) prominently contain elements whose NMR spectra are difficult or impossible to measure at low fields, because the nuclei have spin quantum numbers greater than 1/2 (e.g., ^{7}Li, ^{17}O, ^{27}Al). These nuclei possess electric quadrupole interactions, which are averaged out to lowest order by MAS but make a second-order contribution to the NMR line widths that is inversely proportional to the magnetic field strength. For these reasons, NMR spectra of many technologically important materials are useful only if very high field equipment is used, and are increasingly informative as the field increases.

3. Recent trends and achievements in NMR

In studies of biological systems, NMR is one of the two major types of measurements that can be used to reveal the full 3D molecular structures of macromolecules, especially proteins and nucleic acids, the other being X-ray diffraction measurements on single crystals. In addition to purely structural information, NMR measurements have the unique capability of providing detailed, site-specific information about molecular motions in macromolecules, including motions that are essential for biological function. While X-ray diffraction measurements are largely restricted to highly structurally ordered molecules in crystalline environments, NMR methods are applicable to proteins and nucleic acids in fluid environments that more closely resemble the cytoplasmic and membrane environments of cells. Perturbations of NMR signals due to intermolecular interactions are used in the screening of molecular libraries for binding to pharmaceutically important macromolecular targets, providing an efficient approach to the identification of new lead compounds in drug development. NMR methods are also applicable to molecules that are intrinsically disordered, resistant to crystallization, and (in the case of solid state NMR) inherently non-crystalline and insoluble.

Since the first demonstrations of protein structure determination by NMR in the early 1980s, a series of methodological and technological advances have contributed to a steady increase in the size and diversity of systems that can be characterized by NMR. Among these are the development of multidimensional NMR techniques that allow NMR frequencies of essentially all ^{1}H, ^{15}N, and ^{13}C nuclei within a protein or nucleic acid to be measured and assigned to specific atoms, the identification and characterization of a variety of nuclear spin interactions that can be measured through NMR signals and interpreted as experimental constraints on molecular structure, and the development of highly stable and homogeneous superconducting magnets with fields up to 23.5 T. Some of the most significant new trends in biomolecular NMR that have appeared since the 2005 COHMAG report include: