Instrumentation for High-Field Dynamic Nuclear Polarization NMR Spectroscopy

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1.0 Introduction

The dynamic nuclear polarization nuclear magnetic resonance (DNP NMR) phenomenon was predicted by Overhauser in 1953[1] and confirmed experimentally by Carver and Slichter.[2,3] Initially, the technique was restricted to low-field measurements and thus considered a niche application due to its limited practical applications. However, the advent of high-frequency microwave sources in the past 30 years has allowed the use of the technique for high-field NMR magnets, leading to explosive developments for the technique.[4] Here we present an overview of the important developments in the instrumentation for this rapidly developing spectroscopic field with applications in numerous areas, such as analytical chemistry,[5,6] biological science[7-11] and materials science.[5,8,12,13]

Figure 1 illustrates a modern custom-built high-field DNP NMR installation. The key components, discussed in detail in the following sections are: (1) a microwave source with its associated controller and magnet, (2) a transmission line to deliver high-power microwaves from the microwave source to the NMR probe, (3) the DNP NMR probe, (4) the magic-angle spinning (MAS) controller along with the special rotors required for DNP and the cryogenics gas source and finally (5) the NMR magnet and console. With the exception of the latter, the hardware illustrated here is either not found in a typical NMR lab or is significantly different. Hence, in the ensuing sections, these components are discussed in detail. Finally, we conclude with a discussion on advances that one may anticipate in the near future.

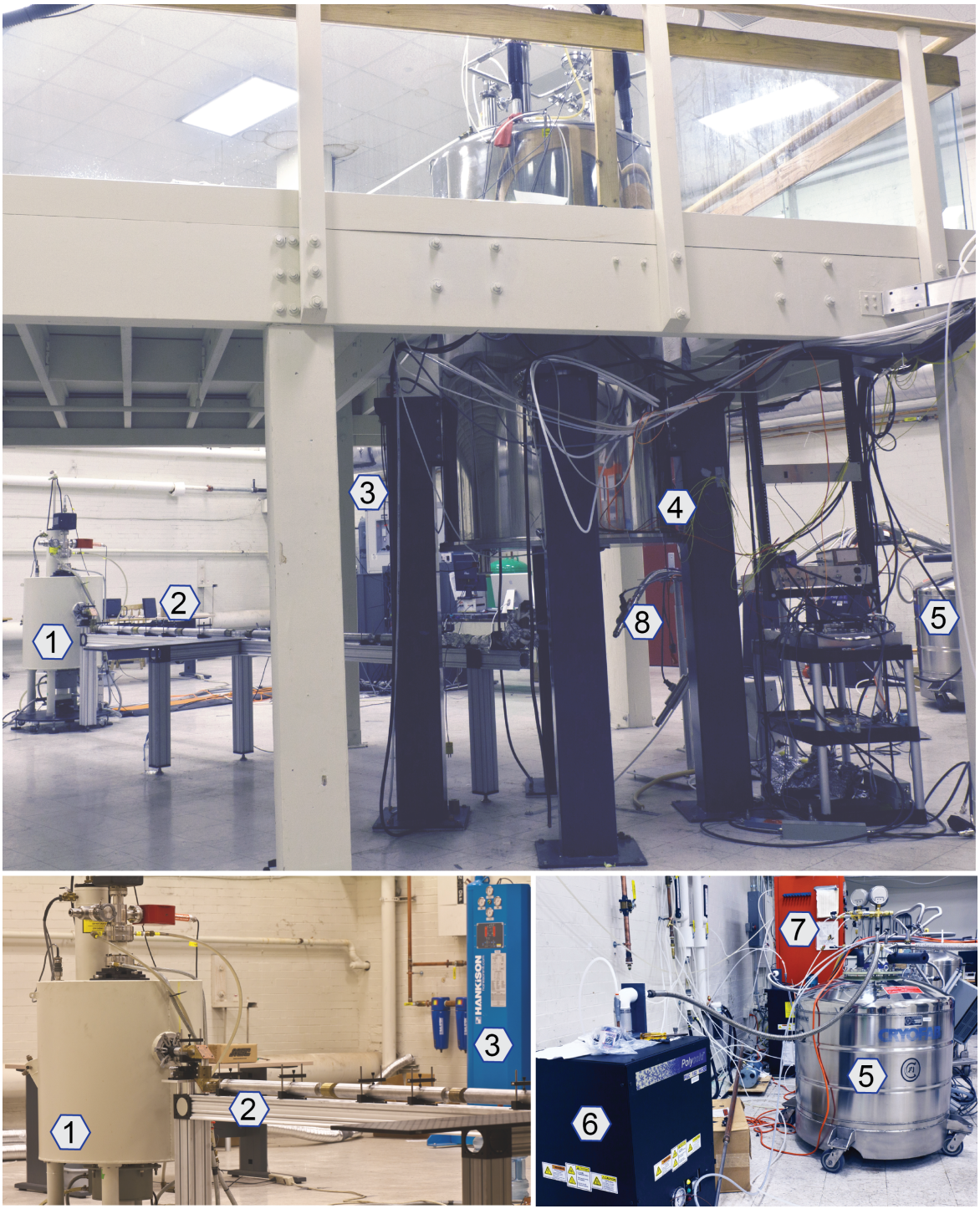

Figure 1. Modern custom-built DNP NMR installation (700 MHz / 460 GHz, FBML-MIT). 1: gyrotron and its magnet; 2: waveguide; 3: N_2 gas separation system; 4: NMR magnet; 5: cryogen dewar; 6: refrigeration (chiller) unit; 7: VT controller and 8: vacuum-jacketed cryogenic gas transfer lines (drive, bearing, VT).

Since the focus of this article is on instrumentation, a detailed discussion of the background theory is beyond the scope of this article; readers are encouraged to consult associated articles within this book as well as several detailed reviews on DNP theory[4,14-20] and related concepts, such as enhancement factors,[21-23] and polarizing agents.[4,15,17,23,24] Readers are assumed to understand the fundamentals of solid-state NMR[25-30] and EPR[31-36] spectroscopy and should consult the many texts on the topics for further details. Note that this article discusses the instrumentation required for DNP NMR of solid samples. DNP NMR for solutions is possible, although the method poses additional challenges.[14,17,37] In dissolution NMR, one hyperpolarizes a frozen sample as for solid samples, then dissolves it; the NMR spectrum is then acquired.[38-41] The hardware requirements for this[39,42] and other solution DNP NMR[43] techniques have been discussed.

2.0 Components of a DNP NMR System

2.1 The Microwave Source

Combining the improved resolution of high magnetic fields with the greatly improved sensitivity afforded by DNP has been a long-term goal for NMR spectroscopists.[44] The fundamental DNP experiment entails the saturation of EPR resonances via microwave irradiation. Since the ratio of the Larmor frequency for the electron to that for ^{1}H is approximately 660, the microwave frequencies must be in the GHz range for virtually all NMR applications (an interesting exception, not discussed further here, is DNP NMR spectroscopy undertaken at Earth's field, where the electron-^{14}N hyperfine coupling of 131.5 MHz, in a polarizing agent at 10 mT, was used to polarize ^{1}H).[45] For many years, the development of microwave sources capable of generating the required frequencies lagged behind advances in

high-field NMR magnet technology, precluding the routine application of DNP at high fields,[46,47] although some work-around solutions were proposed. For example, Dorn *et al*. enhanced the NMR signal *via* DNP at 0.34 T (*i.e.*, requiring a 9.4 GHz microwave source), then, to improve resolution, transferred the sample to a 4.7 T NMR instrument.[48] Although the method provided the desired enhancement, technical difficulties hindered a general application of these and related techniques. Other researchers obtained high-frequency microwave sources, albeit at low power and at very low temperatures. For example, in 2002, Brill proposed an ENDOR-DNP approach, achieving 50 % polarization at 1 K and B_0 = 5 T.[49] Using a similar approach, Morley et al. achieved an enhancement of 10^3 for ^{15}N NMR spectroscopy of $^{15}N@C_{60}$ at B_0 = 8.6 T.[50] Tycko and coworkers[51] obtained an enhancement factor of 80 for a glycerol/H_2O sample using a 30 mW microwave system effectively operating at 264 GHz in conjunction with a 9.39 T magnet (400 MHz ^{1}H).

In the 1990s, extended interaction oscillators (EIOs) or extended interaction klystrons (EIKs) were applied for the desired high-frequency microwaves. These are linear-beam devices, but unfortunately, the power required for DNP NMR spectroscopy at high magnetic fields reduces the lifetimes of these devices,[15] and extending their frequency range beyond those required for 5 T magnets remains a challenge. Despite some drawbacks, they remain the preferred option for certain systems. For example, Dupree and coworkers recently described a tunable 187 GHz EIK amplifier as a microwave source for a DNP NMR system.[52] Likewise, Thurber and Tycko obtained enhancement factors in the 100 – 200 range for ^{13}C NMR signals using an EIO with an output power of 1.5 W as the microwave source.[53] In addition, a 263 GHz EIK is offered by Bruker as an option for their 263 GHz/400 MHz DNP NMR system.

A major breakthrough in high-field DNP NMR spectroscopy came from the Francis Bitter Magnet Laboratory at MIT,[20,44,54,55] where a cyclotron-resonance maser (i.e., a gyrotron) was adapted to operate at the times and power levels required for high-frequency, high-power microwave radiation that enabled DNP NMR at a ^{1}H frequency of 211 MHz (i.e., B_0 = 5 T). The gyrotron is used to stimulate cyclotron radiation, generated within a superconducting magnet,[8] as the microwave source. Although the gyrotron was invented over 50 years ago,[56] use of this device, which typically operated at higher powers to generate microsecond pulses, required modifications to permit continuous wave (CW) operation.[54] DNP NMR devices operating at up to 460 GHz have since been developed by Griffin and coworkers and by Idehara et al.[57] allowing spectroscopy at a 700 MHz ^{1}H frequency. In addition, Temkin and coworkers developed a 20 W, 527 GHz gyrotron suitable for DNP NMR at a ^{1}H frequency of 800 MHz.[58] The success of these and other research groups prompted Bruker Biospin, in collaboration with Communications & Power Industries (CPI), to market DNP NMR systems, with gyrotrons operating at frequencies up to 593 GHz (i.e., 900 MHz ^{1}H). Other commercial sources for gyrotrons have been used (see, for example References 37 and 59) but these are not marketed as complete DNP NMR instruments. Further details about high frequency microwave devices can be found elsewhere in this book.

The DNP NMR experiment requires matching of the EPR and NMR frequencies, a significant complication since EPR signals at a given field strength cover a large frequency range, depending on the polarizing agent. This issue has generally been addressed through the use of sweep coils (vide infra) but there has been recent progress in implementing frequency-tunable gyrotrons, which would alleviate the necessity for sweep coils and the complications associated with these. Relatively small frequency ranges (approximately 100 MHz) have been

achieved by adjusting the temperature in the cavity circuit.[60] Larger tuning ranges (1.2 GHz) have been achieved,[61,77] but challenges, such as varying output power, remain.[4] Tuning ranges greater than 2 GHz have recently been reported by the Griffin laboratory,[62,63] who suggested that combining a tunable NMR magnet with a tunable gyrotron would enhance efficiency, and by Idehara and coworkers;[64,65] the latter also reported that the output power was not stable over the gyrotron frequency range.[64]

The hyperfine interaction arising from the polarizing agent may have undesirable effects on the NMR spectra of samples acquired under MAS conditions, leading to paramagnetic quenching (i.e., loss of intensity).[22] Similar to the situation for routine cross polarization NMR spectroscopy, where ^{1}H decoupling leads to increased resolution in the NMR spectra,[66] decoupling of the hyperfine interaction offers the potential of increased resolution and longer nuclear relaxation times in NMR spectra acquired with MAS and DNP NMR, and may improve the polarization enhancement.[67] Thus, the Barnes research group has been working extensively in the area of hyperfine decoupling.[68-71] Development is ongoing but promising results have been reported. For example, ^{13}C NMR linewidths were reduced by 11 % and the signal intensity increased by 14 % using microwave frequency sweeps through the EPR pattern (Figure 2).[68]

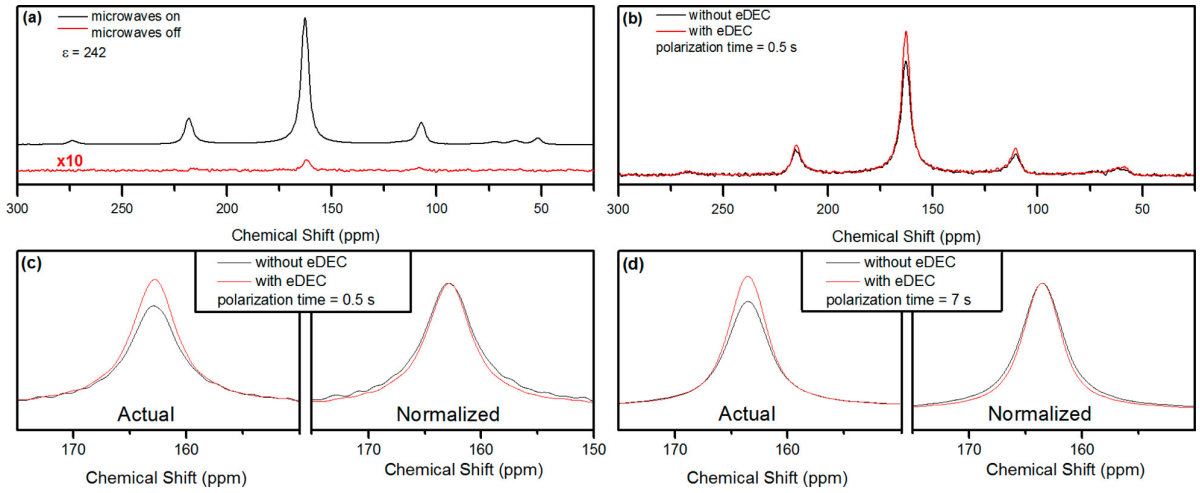

Figure 2. Comparison of NMR spectra of urea acquired with and without DNP (a) and with DNP but with or without electron decoupling (b-d).[68] Reprinted with permission from reference 68. © 2017, American Chemical Society.

Optimum signal enhancement is achieved when all electrons in the polarizing agent are irradiated.[72] Some agents with large *g*-anisotropy have large inhomogeneous EPR linewidths, which increase at higher magnetic fields.[73] Hence, if DNP NMR measurements are conducted with continuous wave irradiation of the polarizing agent at a constant field, only a fraction of the electrons are irradiated, particularly in the absence of MAS. Frequency sweeps have been used but the method frequently is inefficient.[72] Hovav et al. used microwave frequency modulation to irradiate a broader bandwidth,[74] obtaining a three-fold improvement on the enhancement, compared to that obtained in the absence of frequency modulation. Recently, Pines and coworkers demonstrated that improved polarization of agents with broad bandwidths may be achieved through the use of microwave frequency combs.[72] The method involves simultaneously sweeping the entire electron linewidth with the "teeth" of the comb (Fig. 3).

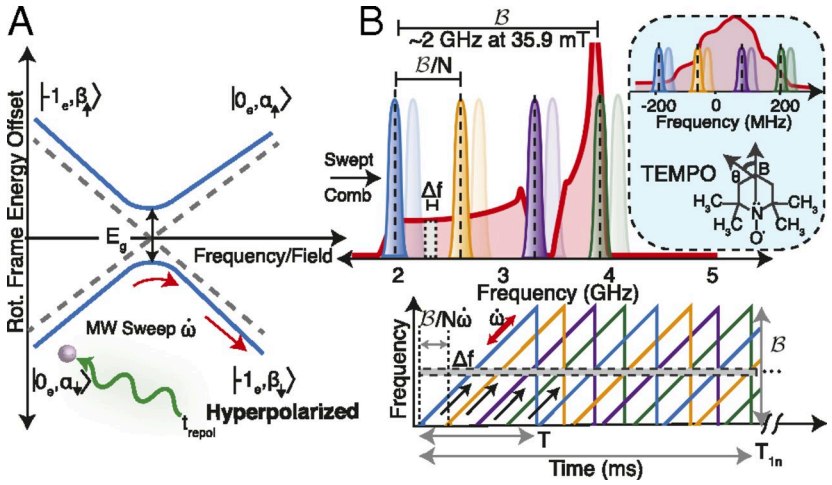

Figure 3. Frequency comb used for DNP enhancement. In (A), the hyperpolarization process using the frequency/field swept techniques is illustrated. (B): the red trace illustrates the inhomogeneously broadened electron spectrum (with line width of *B*) arsing from nitrogen vacancy center defects in diamond. The frequency comb, allowing repeated polarization transfers, is illustrated at lower right. The inset illustrates the TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) polarization agent as well as its electron spectrum, another good candidate for the technique. Copied, with permission, from reference 72. © 2018, National Academy of Sciences.

2.2 The Waveguide

Another significant challenge in DNP NMR spectroscopy is the transmission of the microwaves, generated as discussed above, to the sample. Since current technology requires that the gyrotron magnet be situated at a distance from the NMR magnet, the microwaves must be transmitted over several meters while minimizing losses.[20,44,47,59,75-78] For example, the waveguide used at the Francis Bitter Magnet Laboratory is a 4.65 m corrugated waveguide with an inner diameter of 19.05 mm.[47,77] Currently, the favoured technology is the use of corrugated over-moded waveguides,[77,79] which are more efficient than fundamental-mode rectangular waveguides.[47] Part of the output from the waveguide must be diverted to determine the output frequency.[77] Hill and coworkers have described a waveguide equipped with a splitter, permitting simultaneous DNP NMR measurements on two 14.1 T NMR magnets.[76] It of course is not possible to transmit the

microwaves in a direct line from the gyrotron to the sample within the NMR magnet, so a series of high precision miter bends are required within the waveguide;[8] reducing the number of bends is highly desirable to minimize complications and potential losses in power and beam structure.[59]

Quasioptical transmission systems have been proposed as an alternative to the corrugated waveguide described above.[8,80,81] In this setup, the microwaves are transmitted via mirrors. The method allows more flexibility, such as power attenuation and beam splitting.[8]

2.3 The NMR Probe

In addition to the functionality typically associated with conventional MAS NMR probes (e.g., stable high-frequency spinning, accurate setting at the magic angle), the corresponding DNP NMR probes have additional requirements.[4,59] They must allow much lower-temperature operation and hence gas lines within the probe must be insulated, typically with a vacuum jacket. In fact, some DNP probes are vacuum jacketed to maintain a cool internal temperature while protecting the NMR magnet bore from these low temperatures. The stator housing must accommodate the microwave transmission line (vide supra). In addition, the ability to eject and insert samples with the probe at low temperature is important for high-throughput studies, since several hours are required to cool the probe to operating temperatures of approximately 100 K and then to heat it back up to room temperature.[79,82] Figure 4 illustrates a modern custom-built DNP NMR probe and stator.

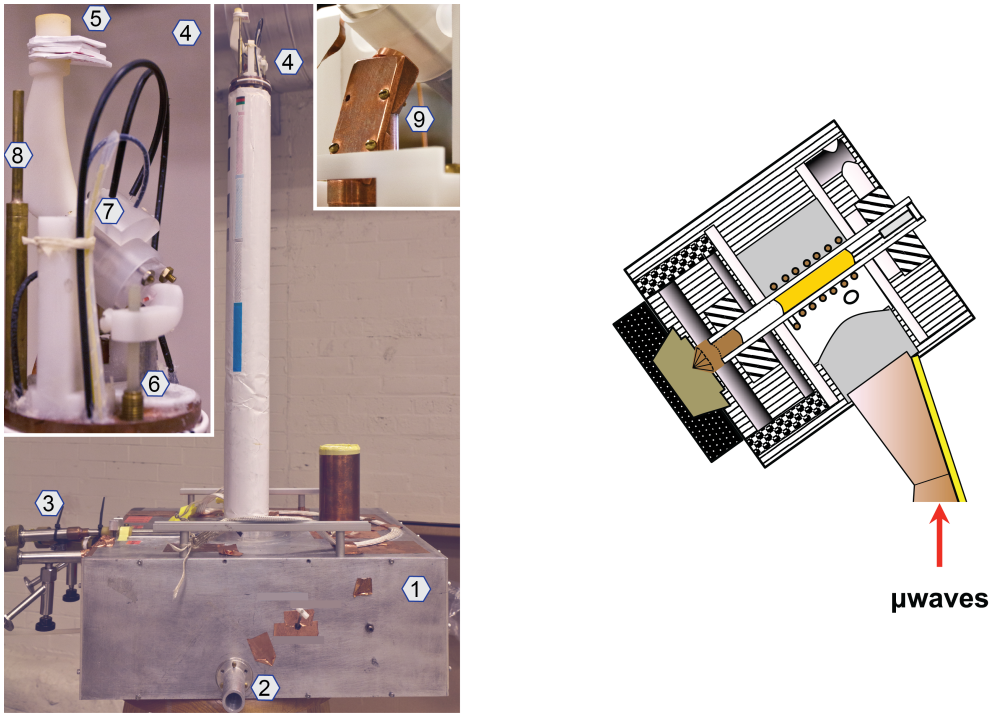

Figure 4. Photographs of an NMR probe and expanded view of some of its components (left). 1:NMR probe; 2: waveguide; 3: insulated bearing and drive gas lines; 4: probe head, 5: sample insert/eject; 6: magic angle adjust; 7: stator; 8: variable temperature (VT) gas line; and 9: waveguide to the sample. At right, a schematic representation of a rotor and stator, adapted from Reference 83, is shown.

In a typical DNP NMR setup, the microwaves are delivered to the sample from the bottom of the probe, and then directed through a series of miter bends such that they strike the sample orthogonal to the MAS rotor axis (Fig. 4). In this configuration, the microwaves must traverse the NMR radio frequency coil, adversely impacting their enhancement effects.[84] Nanni et al. have shown that these effects can be minimized by adjusting the coil spacing.[84] Alternate designs have been proposed.[59] For example, the systems developed by Horii and coworkers[85] and by Pike *et al*.[81] deliver the microwaves from the top of the probe and direct them to the top of the rotor. This configuration allows the probe to be quickly removed or installed and saves space within the probe body since the waveguide is external to it.[81] With the latter schemes, the microwave irradiation is parallel to the rotor axis and is sensitive to constraints imposed by the MAS

system.[59] In addition, sample penetration is imperfect when the microwaves are introduced from the top of the rotor. Other designs are currently being investigated (see reference 59).

2.4 Magic Angle Spinning: Gas Sources, Rotors and Controllers

As for other solid-state NMR experiments, MAS has the potential to greatly improve the resolution of the spectra that are obtained with DNP. Unfortunately, in the latter studies, MAS may also induce depolarization, negating some of the advantages of DNP.[86-88] Careful selection of polarizing agents have mitigated the problem.[86,89] A further concern is that the problem may worsen as the spinning frequency increases,[90,91] thus further radical development is ongoing. In their investigation of this effect, Emsley and coworkers obtained indirect ^{29}Si DNP NMR spectra in the 10 to 40 kHz range and found that, although the depolarization does indeed increase with spinning frequency, the benefits of DNP and rapid MAS outweigh the disadvantages: a significant fraction of the sample still contributes and yields an enhancement and the higher spinning frequency increased the coherence lifetimes of the material under investigation.[90] With the assistance of computer simulation programs, De Paëpe and coworkers recently prepared a series of polarizing agents that show little or no depolarization at high MAS frequencies.[91]

Another important requirement of a DNP NMR lab is the source of MAS and VT gases. DNP experiments are typically performed at low temperatures to improve electron and nuclear relaxation behavior and hence to improve the transfer of polarization to the nuclei.[15,92] Sustained low-temperature MAS imposes numerous challenges; in particular, gas flow rates must be varied depending on the desired spinning frequency and the mass of the sample, rendering temperature regulation more difficult.[59,93,94] Continuous operation at temperatures near 90 K has been achieved with the use of nitrogen gas as the bearing and drive gas sources while simultaneously

providing the sample temperature regulation. The gas may be sourced from large (150 or 220 L) dewars; two such dewars ensure that data acquisition is not disrupted when one dewar's supply is exhausted,[93] but a disadvantage of this system is that the high pressures required for NMR at high MAS frequencies means that large quantities of liquid nitrogen are consumed, driving costs; a typical DNP NMR setup may use several hundred liters per day. Matsuki et al.[95] as well as Griffin and coworkers[46] have used an N_2 gas separator in conjunction with an electric chiller to generate low-temperature gas which is then chilled by liquid N_2. The authors report that this strategy reduces nitrogen consumption by a factor of four compared to the consumption experienced under the same conditions using N_2 boil-off as a gas source.[95]

Another complication with N_2 as a VT gas is that its viscosity increases as the liquefaction point is approached, precluding its use for MAS NMR spectroscopy at lower temperatures.[4] Hence, lower temperature MAS has been achieved with helium as the VT gas source and as the liquid heat exchange medium,[94,96] although this comes with additional challenges.[15] To minimize the prohibitive costs of helium, Thurber and Tycko developed an MAS system whereby the bearing and drive gases were obtained from N_2 while helium was used as the VT gas; longer rotors were used to isolate the VT helium gas stream from that for nitrogen.[53,97] Closed-loop helium recirculation systems have been designed.[98-100]

In room-temperature MAS NMR spectroscopy, stable spinning is achieved through regulation of the bearing and drive gas pressures, typically using MAS controllers one routinely finds in solid-sate NMR labs. This hardware is suitable for DNP NMR applications, since the drive and bearing gases are cooled down the line from the MAS controller.[4] After exiting the MAS unit, the gases, along with the VT gas, are cooled to the target temperature inside a pressurized heat exchanger.[4] To maintain temperature stability, the gas transfer lines from the

heat exchanger to the probe are vacuum jacketed. Control of the cooling capacity is achieved by a heat exchanger that permits the replenishment of liquid nitrogen during operation.[82] A more recent design use separate heat exchangers for the drive, bearing and VT gas streams, allowing greater flexibility in experimental conditions.[4] As discussed above, liquid helium must be used as the heat exchange medium for temperatures below approximately 90 K.[4]

The NMR rotors must permit effective transmission of microwaves into the sample, while being robust enough to handle low temperatures as well as the excessive forces associated with high spinning frequencies (> 5 kHz). Typically these are made of sapphire[60,82,101] or of zirconia (i.e., the material typically used for solid-state NMR rotors). While the latter are more robust,[15] sapphire rotors are transparent to microwave radiation and have high thermal conductivity, an important consideration for samples that must be cooled to 100 K or lower.[82] In addition, greater signal enhancements have been reported when sapphire rotors were used.[60,101] Until recently DNP NMR measurements were undertaken primarily with 3.2 or 4.0 mm outer diameter rotors, but, as discussed above, faster spinning DNP NMR probes are being developed.[90] A commercial (Bruker) 1.9 mm DNP NMR probe permits sample spinning frequencies of up to 25 kHz at 100 K, and permits sample changes while the sample is cold. This manufacturer also offers a 1.3 mm probe, permitting MAS experiments at 40 kHz, at approximately 115 K.[102] These rotors of course have smaller sample volumes, but the loss of signal from this factor is mitigated by the greater microwave penetration and hence the improved DNP enhancement. For non-spinning applications, quartz EPR tubes have been used as well.[50,55]

Recently, Barnes and coworkers have demonstrated the benefits of using spinning spheres rather than cylindrical rotors for DNP NMR samples.[103] The authors demonstrate that such spheres provide stable sample spinning and improved signal to noise ratios while conserving

space within the probe head. Another benefit of spinning spheres is that a single gas stream is required for the bearing, drive and VT gases.

2.5 The NMR Spectrometer

The basic NMR spectrometer, with the exception of the probe discussed above is that used for solid-state NMR spectroscopy, but a wide-bore (i.e., 89 mm) magnet must currently be used to accommodate the hardware, such as the waveguide and electronics, insulation, variable temperature lines, and vacuum jacketed dewar associated with DNP applications at cryogenic temperatures.[15] Likewise, the NMR console is that used for solid-state NMR applications.

As discussed above, there has been significant progress in frequency-tunable gyrotrons. Nevertheless, because of continuing challenges with these means, sweepable NMR magnets are often used to achieve the desired electron/nucleus frequency ratio.[4] This is commonly accomplished by coupling the NMR magnet with a superconducting sweep coil;[104-106] however, challenges remain for this technique as well. For example, the sweep rates are limited and may lead to temporary field instability and excess cryogen consumption through He boil-off. In addition, the sweepable range remains limited; that reported by Kaushik et al. has a sweep range of ±75 mT[106] and hence there are still cases where it is not possible to achieve the matching conditions for some polarizing agents, such as some metal ions.[4]

3.0 Future Developments

Despite the extensive recent developments, many avenues of research in DNP NMR remain open. For example, the behavior underlying certain mechanisms causing the DNP phenomenon is not fully understood.[107] While the complex interplay of factors governing the DNP efficiency means that the theoretical maximum enhancement factors are unachievable,[23] there surely is much room for improvement, as attested by the quantity of recent articles published in recent months addressing these issues.[23,91,108-111]

Developments in other areas are also promising. As discussed above, the requirement for cryogens is a major driver of costs for DNP NMR. In addition to recent developments discussed above, Scott et al.[112] have developed a cryostat-transfer line system that increases the efficiency of DNP NMR measurements below 6 K. Alternatives are being investigated. Eichorn et al. have presented preliminary results whereby the electron spins needed for the DNP process are obtained through a photoexcitation process.[113] Results are promising, albeit at a relatively low field (0.3 T).

The requirement for a gyrotron source located at a distance from the NMR magnet is a significant complication for a DNP NMR lab, particularly since another superconducting magnet is required, for the gyrotron. In the hope of avoiding the necessity for a second superconducting magnet, Bratman et al. described a DNP NMR system that incorporates the gyrotron within the NMR magnet.[114] Since the presence of a standard power gyrotron (10 – 20 kV) within an NMR magnet would compromise the field homogeneity, the authors developed a low-voltage gyrotron.[115] Although development work remains, the approach is promising. Likewise, Ryan and coworkers also recently discussed advances in the goal of integrating a gyrotron into an

NMR magnet.[116] The gyrotron is located immediately above the NMR probe; to avoid the requirement for slightly different field strengths for the gyrotron and NMR probe, a ferroshim assembly is proposed for the latter. Although still under development, the method offers that hope that the infrastructure required for a DNP lab may in the future be significantly reduced.

A major feature of modern NMR spectroscopy is the advent of magnets with increasing magnetic field strengths. Commercial magnets up to 23.5 T (1.0 GHz, ^{1}H) are currently available, with 1.1 and 1.2 GHz instruments on the horizon. This begs the question, can DNP keep up? Combining the high resolution benefits of the high-field NMR magnets with the potential sensitivity of DNP is very appealing, but challenges must be overcome. In particular, the cross effect, which is the major mechanism used in current DNP NMR applications, scales inversely with field.[88] Another challenge is that it is desirable to spin samples at higher frequencies when obtaining NMR spectra at higher magnetic field strengths, but, as discussed above, this introduces further complications in the polarization transfer mechanism.[90,91] Another challenge is the requirement for higher frequency gyrotrons,[4,24,59,117,118] and of course, as with NMR spectroscopy in general, higher magnetic fields come at a higher cost. Despite such challenges, DNP NMR results at 21.1 T have been reported.[102,119]

4.0 Concluding Remarks

The promise of DNP NMR is highlighted by the high interest shown in the technique and by the fact that several articles, either using the technique or proposing to improve the technique, appear each week. Despite the numerous DNP NMR labs now found, particularly in Europe and North America, it is surely to early to describe DNP NMR as a mature research field, since the pace of

rapid development in instrumentation and methodologies observed over the past two decades shows no sign of abating, as demonstrated by the number of recently published articles cited in this review. The method will one day reach a point where development is incremental at which point it may be considered a mature field, taking its place in the experimentalist's toolkit for unraveling the mysteries of nature. However, that point has not been reached yet: the near future promises many more exciting developments!

Biographical Sketches

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