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# A new approach to enhancing the sensitivity of solid-state NMR

## Magic-angle spinning

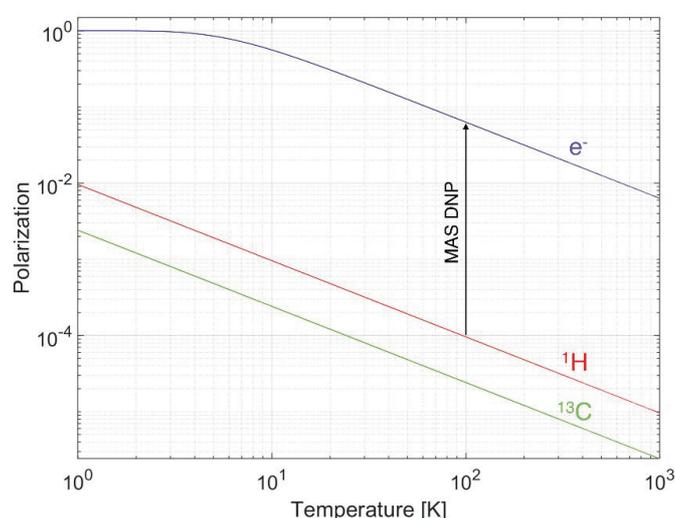
In liquids, rapid motion and tumbling of molecules effectively removes anisotropic interactions between nuclear spins and magnetic fields. For this reason, liquid-state nuclear magnetic resonance (NMR) spectra naturally have narrow spectral lines and high resolution. NMR spectra of solids, on the other hand, have – because motion is restricted – broad features and poor resolution. Informative, high-resolution NMR spectra of solids can nevertheless be obtained with the help of magic-angle spinning (MAS). In a MAS NMR experiment, the sample is packed into a rotor and spun rapidly around an axis at  $54.7^\circ$  with the external magnetic field – this removes anisotropic interactions, much like rapid tumbling in liquids.

The concept of MAS dates back to the 1950s, [1, 2] but it took decades for MAS NMR spectroscopy to mature as a method to investigate the structure and dynamics of solids. A critical step was the development of radio wave pulse sequences to selectively suppress or reintroduce dipolar couplings, often referred to as de- and recoupling. Ingenuity of engineering made the MAS NMR experiment robust, and fast – nowadays spinning frequencies over 100 kHz are used. The strength of MAS NMR lies in its ability to provide specific, atomic-level structural information on complex chemical systems for which this is notoriously difficult to obtain, including weakly ordered or membrane-bound proteins and amorphous materials. MAS NMR is non-invasive, allows structures to be investigated in their native states, and provides information on functionally relevant, local dynamics.

## Enhanced polarization and sensitivity

The energy separation of the two magnetic sublevels of a spin-1/2 particle is proportional to the strength of the applied magnetic field. In frequency units, the separation is given by  $\omega_0 = -\gamma B_0$ , with  $\omega_0$  the Larmor frequency,  $\gamma$  the gyromagnetic ratio of the spin species, and  $B_0$  the magnetic field. In thermal equilibrium, a small difference between the populations of the magnetic sublevels arises, according to the Boltzmann

distribution. This produces a macroscopic magnetic moment, which is manipulated and detected in an NMR experiment. The strength of the NMR signal thus depends on this population difference, which is conveniently quantified, independently of sample size, by the polarization, see Figure 1.



**Fig. 1:**  $e^-$ ,  $^1\text{H}$ , and  $^{13}\text{C}$  spin polarizations at 9.4 T/400 MHz/263 GHz as a function of temperature. Polarization is defined as the difference between the populations of the lower and upper magnetic sublevels divided by the total number of spins in the sample, e.g., for  $^1\text{H}$  spins

$$P_{^1\text{H}} = \frac{N_- - N_+}{N_- + N_+} = \tanh\left(\frac{\gamma_{^1\text{H}} \hbar B_0}{2k_B T}\right).$$

Figure 1 illustrates that at the temperatures and magnetic field strengths of a typical NMR experiment, only a very small fraction of the nuclear spins in the sample contributes to the signal. This situation can be drastically improved by doping the NMR sample with a paramagnetic species or “polarizing agent” and applying microwave irradiation at or near the electron Larmor frequency. The microwaves induce a transfer of electron spin polarization from the polarizing agents to nearby nuclear spins (preferably  $^1\text{H}$ s) via the hyperfine coupling. The network of dipolar-coupled nuclear spins (again preferably  $^1\text{H}$ s) in a solid allows the polarization to diffuse into the sample and, in this way, the polarization of the bulk nuclei is enhanced. This is referred to as dynamic nuclear polarization (DNP) and it can be used to improve the sensitivity of NMR by 2 to 3 orders of magnitude.

The size and complexity of molecular structures that can be investigated with MAS NMR spectroscopy is in practice restricted by the signal-to-noise ratio (SNR) of the spectra one can obtain within a reasonable amount of time. As the SNR increases only with the square root of the number of acquisitions used for

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DOI-Nr.: 10.26125/ppzr-tr96

averaging, the extra sensitivity provided by DNP has drastically extended the scope of MAS NMR, particularly in materials science. DNP has enabled direct observation of species that occur at inherently low density, such as catalytic sites in porous materials, as well as advanced correlation experiments on “challenging” nuclei which are, without DNP, difficult to detect due to a low gyromagnetic ratio, low isotopic abundance, or a large quadrupolar interaction.

The majority of current MAS DNP studies relies on commercial instrumentation, which first became available about 15 years ago. [3] This instrumentation follows the original experimental design developed in the research groups of Griffin and Temkin at MIT in the 1990s. [4] The temperature of the experiment is lowered to about 100 K, using liquid N<sub>2</sub> as a cryogen, and polarizing agents are homogeneously dispersed in a frozen glassy matrix. [5] Active DNP mechanisms are the solid-effect and/or the cross-effect, two classical mechanisms which rely on continuous (CW) microwave irradiation at high-power. [6, 7] Dedicated gyrotrons [8] provide this microwave or, more precisely, sub-THz irradiation continuously at tens of Watts, nowadays up to 592 GHz (matching a <sup>1</sup>H Larmor frequency of 900 MHz at 21.1 T). The cross-effect, which relies on two interacting electrons, maintains its efficiency considerably better than the solid-effect as the magnetic field is increased, particularly when biradicals are used as polarizing agents, [9] and is used in most applications. However, even with the help of sophisticated hetero-biradicals, [10] it remains a challenge to maintain sensitivity enhancements at the highest magnetic fields.

**Pulsed dynamic nuclear polarization**

MAS DNP, in its current form, established DNP as a means to enhance the sensitivity of NMR and helped MAS NMR spectroscopy to reach a new level of maturity. DNP methodology can, however, in all likelihood be improved. In particular, what comes to mind is a transition from CW DNP to DNP induced by a microwave pulse sequence, i.e., to pulsed DNP. This would be analogous to the transition from CW NMR to pulsed NMR, and from CW electron paramagnetic resonance (EPR) to pulsed EPR, which opened up many new, unforeseen possibilities for both branches of magnetic resonance spectroscopy. [11, 12] Moreover, pulsed DNP may prove to be a generally superior and more robust way to enhance the sensitivity of high-resolution MAS NMR, for two reasons. First, the effective Hamiltonian, which describes polarization transfer during the pulse sequence, is field independent. Hence, pulsed DNP is expected to maintain its efficiency at high magnetic fields. Second, as microwave irradiation is applied only briefly during the pulse sequence, pulsed DNP operates at low average power. This reduces sample heating, which becomes noticeable, even for frozen solutions, as wavelengths drop below 1 mm (263 GHz).

Figure 2a shows the general scheme of pulsed DNP. The DNP sequence induces a rapid transfer of polarization from the polarizing agents to nearby <sup>1</sup>Hs, within a few 100 ns to a few μs. The microwaves are then switched off and the electron spins relax back to equilibrium, typically within 1 ms. Meanwhile the enhanced polarization diffuses into the sample. The pulsed

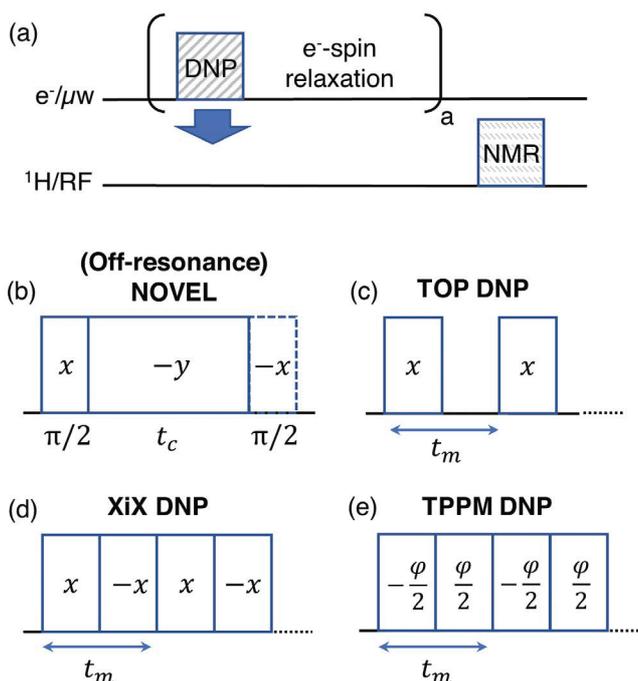


Fig. 2: (a) General scheme for pulsed DNP. (b-e) Possible sequences to be applied during the DNP block in (a).

DNP cycle is repeated thousands of times to build up bulk dynamic nuclear polarization for each NMR measurement.

Figures 2b-e show known DNP pulses sequences. Just like de- and recoupling sequences in MAS NMR, these sequences exploit interference effects between time dependencies in the Hamiltonian of the spin system. A sequence is designed such that in the effective Hamiltonian only the desired interactions remain, while others are averaged out. In the case of pulsed DNP, the dipolar coupling between the unpaired electron of the polarizing agent and a nearby <sup>1</sup>H mediates the transfer of polarization and needs to be preserved as much as possible.

Pulsed DNP was first demonstrated with the NOVEL (Nuclear spin Orientation Via Electron spin Locking) sequence (Figure 2b). [13, 14] In NOVEL, a spin lock is applied to the electron spins at a nutation frequency ( $\omega_{1e} = |\gamma_e B_1|$ ) that matches the <sup>1</sup>H Larmor frequency ( $\omega_{01H} = -\gamma_{1H} B_0$ ):  $|\omega_{1e}| = |\omega_{01H}|$ . The sequence works very well at low magnetic field, e.g., at 0.34 T/15 MHz/9.7 GHz, but at high magnetic fields the matching condition demands unrealistically high nutation frequencies, and hence irradiation powers. The sequence is therefore not suited for pulsed DNP in combination with high-resolution MAS NMR. A first step toward solving this problem was taken with Off-resonance NOVEL. [15] When the electron spins are irradiated slightly off resonance, they nutate at a frequency  $\sqrt{\omega_{1e}^2 + \Omega^2}$ , with  $\Omega = \omega_{0e} - \omega_{\mu w}$  the resonance offset. If this nutation frequency matches the <sup>1</sup>H Larmor frequency,  $|\sqrt{\omega_{1e}^2 + \Omega^2}| = |\omega_{01H}|$ , efficient transfer of polarization is generated with reduced microwave power.

The requirement of a high nutation frequency is further relaxed when the TOP (Time-Optimized Pulsed) DNP sequence (Figure 2c) is used. [16] Under the influence of the pulse train, the electron spin magnetization follows a complex three-dimensional trajectory that will contain two incommen-

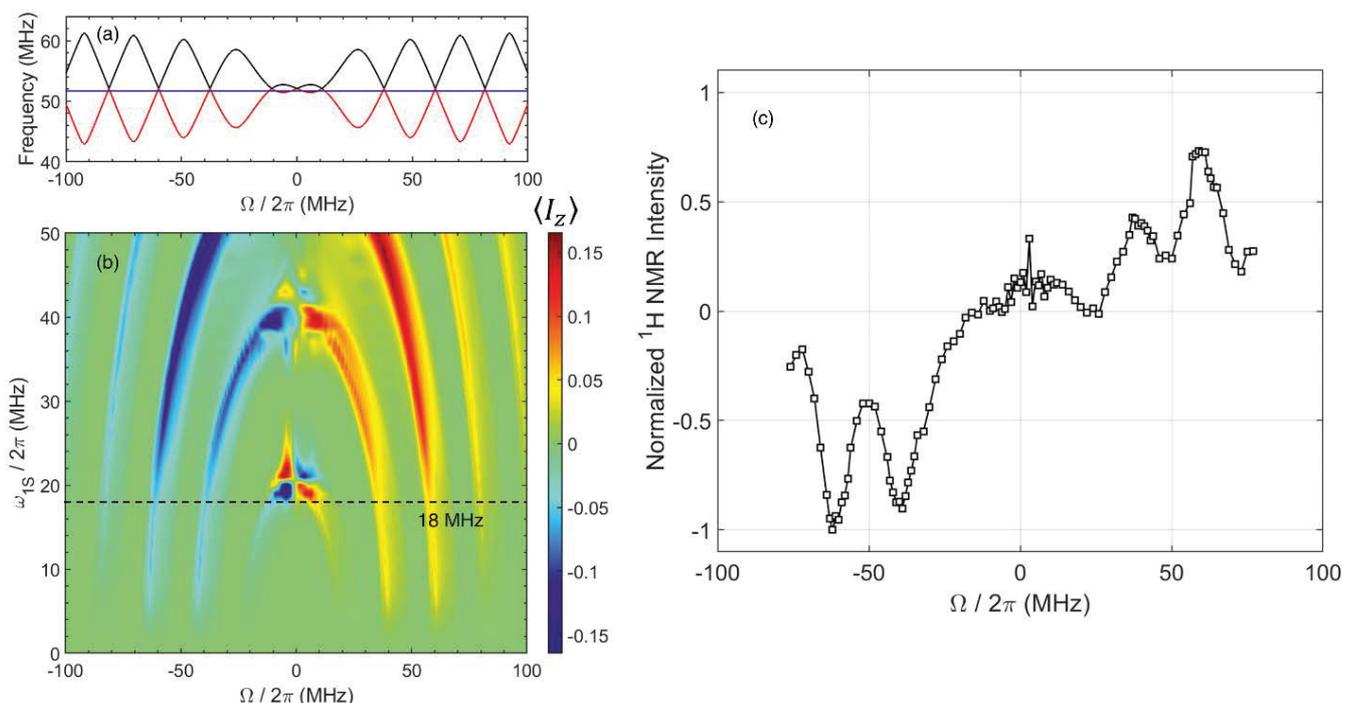
surate frequencies, the modulation frequency,  $\omega_m = 2\pi/t_m$ , and the effective rotation angle per block of the sequence,  $\omega_{\text{eff}} = \beta_{\text{eff}}/t_m$ . The matching condition of TOP DNP takes the form  $n\omega_{01H} + k\omega_m + l\omega_{\text{eff}} = 0$  ( $n, l = 0, \pm 1$  and  $k$  is any integer). In words, polarization transfer takes place when a multiple of the modulation frequency plus or minus the effective frequency matches the  $^1\text{H}$  Larmor frequency. The TOP DNP sequence was found to work well at 1.2 T/51 MHz/34 GHz.

The introduction of TOP DNP, and its matching condition, ended the belief that pulsed DNP at high magnetic field would always require unrealistically high nutation frequencies. A downside of the sequence is, however, that the transfer of polarization is rather slow. This is a property of the TOP sequence – in its effective Hamiltonian, the strength of the  $e^- - ^1\text{H}$  dipolar coupling is reduced to about one tenth of the actual value. We were recently able to improve upon this point with the introduction of two new DNP pulse sequences: XiX (X-inverse-X, Figure 2d) [17] and TPPM (Two Pulse Phase Modulation, Figure 2e) [18] DNP. Both sequences are named after analogous heteronuclear decoupling sequences used in MAS NMR. [19, 20] They obey the same matching condition as TOP DNP, and are therefore high-field compatible, but do a better job at preserving the  $e^- - ^1\text{H}$  dipolar coupling in the effective Hamiltonian. In experiments at 1.2 T, both sequences performed better than TOP DNP, indicating that the rate of polarization transfer indeed matters for the enhancement of the bulk polarization.

The effective frequencies ( $\omega_{\text{eff}}$ ) imposed by the TOP, XiX, and TPPM DNP sequences are characteristic of each sequence and can be calculated analytically. Given a nutation frequency, microwave resonance offset, and pulse (and delay) length,

locations of DNP matching conditions can readily be found. However, the efficiency of the DNP conditions varies drastically – some are not DNP active at all. Hence, we developed numerical simulations (based on the open-source magnetic resonance simulation library Spinach [21]) to screen matching conditions for efficiency. [17] Figure 3 illustrates this for XiX DNP. Simulations and experiments were found to be in good agreement.

To effectively control the electron spins and realize an efficient transfer of polarization in pulsed DNP, one would expect that the nutation frequency must be large compared to the interactions of the electrons with their environment. Indeed, although the matching condition for TOP/XiX/TPPM can be fulfilled even for very small nutation frequencies, numerical simulations suggest that a nutation frequency of 5-10 MHz is minimally needed (Figure 3). Microwave sources that induce such nutation frequencies, by means of coherent pulses, are, with the exception of a prototype at 250 GHz, [22] at the moment not available above  $\sim 95$  GHz. For this reason, it has not yet been possible to investigate pulsed DNP experimentally at magnetic fields relevant for high-resolution MAS NMR. However, the development of sub-THz sources and amplifiers is an active field of research and conversations with microwave engineers have left us optimistic. Low-field pulsed DNP experiments have provided a clear proof of concept and are indispensable for gaining a better understanding. The tools for expanding the repertoire of DNP pulse sequences are on the table. As we will work our way up in magnetic field and obtain feedback from new experiments, it will be possible to adjust sequences to technical and experimental limitations. It seems that a very interesting scientific journey has only just begun.



**Fig. 3:** (a) Plots of  $5v_m - v_{\text{eff}}$  (red) and  $5v_m + v_{\text{eff}}$  (black) for XiX DNP as a function of the resonance offset,  $\Omega/2\pi$ , for a nutation frequency of  $\omega_m/2\pi = 18$  MHz and  $t_p = 48$  ns ( $v_m = 10.4$  MHz). The  $^1\text{H}$  Larmor frequency is 51 MHz (blue). (b) Numerical simulation of XiX DNP. The colors indicate the absolute longitudinal magnetization obtained by the  $^1\text{H}$ s (from the electrons) after the XiX sequence has been applied. (c) Experimentally observed  $^1\text{H}$  NMR signal intensity as a function of microwave resonance offset for XiX DNP at 1.2 T with  $\omega_m/2\pi = 18$  MHz and  $t_p = 48$  ns. Reprinted (adapted) with permission from [17], Copyright 2022 American Chemical Society.

## Acknowledgement

Our research is funded through the Emmy Noether Programme of the DFG.

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Guinevere Mathies studied Physics at Leiden University and obtained her PhD in the same department. She was a postdoctoral research scholar in the Department of Chemistry at the Massachusetts Institute of Technology, supported by a Rubicon fellowship from the Dutch Research Council (NWO). Since 2017 she leads an Emmy Noether Research Group in the Department of Chemistry at the University of Konstanz. Her group develops and applies new spectroscopic methods, based on magnetic resonance, to investigate the structure and dynamics of chemical systems in the solid state.

