# Quantum-enhanced MRI Sensitivity: Dissolution-dynamic Nuclear and Parahydrogen-induced Polarization

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**Abstract.** Contemporarily, magnetic resonance imaging (MRI) has been widely utilized in medical diagnostic. Among various features, the signal intensities serve as the key role in resolution of the detection results. In general, the MRI signal intensities can be substantially increased by several orders of magnitude via dissolution-dynamic nuclear polarization (d-DNP) and parahydrogen-induced polarization (PHIP). This study exhibits the general principles and components of the preparation of these two methods, as well as illustrates the current applications and limitations of d-DNP and PHIP both theoretically and analytically. The experimental conditions, including temperature, magnetic field strength, and whether microwave irradiation is required, are described and contrasted. According to the analysis, the advantages and drawbacks of these two approaches have been compared, along with expectations and outlooks of the future development of quantum-enhanced MRI techniques, in terms of the MRI signal sensitivity. Overall, these results shed light on guiding further exploration of enhancing the resolution of MRI.

**Keywords:** dissolution dynamic nuclear polarization; parahydrogen induced polarization; magnetic resonance imaging; signal amplification by reversible exchange.

## 1. Introduction

Magnetic resonance imaging (MRI) is the three most widely used medical imaging techniques, along with computed tomography (CT) and X-ray scanning, are three of the most widely applied medical imaging technologies. MRI produces three-dimensional detailed anatomical images, especially for disease detection, diagnosis, and treatment monitoring. The general principle is to create a strong magnetic field, which forces the protons in the tested sample to align with the field, and hence to excite protons and scan the change in their spin directions found in the water that makes up soft tissues [1].

In 1882, Nikola Tesla first discovered the rotating magnetic field, but he seldom imagined that this would conduce to the invention of NMR and MRI in around a century. Paul C. Lauterbur and Peter Mansfield, physicists who received Nobel Prize in Physiology in 2003, shall be honored as the fathers of MRI. Indeed, they were the first to apply magnetic field gradients to the localization of nuclear magnetic resonance (NMR) signals [2, 3]. Indeed, Raymond Damadian discovered the concepts of the medical application of NMR in 1971 [4]. Since the 21$^{st}$ century, MRI technology experienced a huge forward leap due to declining costs and better accessibility. In recent years, both theoretical and practical concepts are advanced to conspicuously enhance the performance of MRI. Despite the relatively high resolution in the field of visualizing animal subjects, MRI still suffers from artifacts, such as distortions and no uniformity. MRI and NMR techniques had evolved rapidly in the past few decades [5]. MRI and NMR are increasingly important in chemical analysis and medical diagnosis under their high spatial resolution, wide time response scale, and non-invasive detection.

Yet at an atomic level, the current MRI and NMR technology face serious sensitivity limitations. The low polarization of atomic nuclei conduces the low sensitivity of MRI techniques at this stage. Hyperpolarization is a key component in magnetic field strength and performs a vital role in increasing the MRI signals for diagnosis. It may effectively improve the sensitivity of NMR. Its physical or chemical process pushes the spin state of the nucleus to a state that diverges from thermodynamic equilibrium, resulting in a boost in NMR signal intensity by several orders of magnitude and greatly improving sensitivity [6]. The widely known hyperpolarization methods

involve extreme conditions, including low temperature, catalyst, or strong magnetic field strength. In recent years, the swift advance in quantum computing and quantum sensing provided hyperpolarization a completely new path. The invention of semiconductor qubits benefits hyperpolarization research by requiring room temperature and a relatively lower magnetic field. The recent discoveries of quantum effects in silicon materials had led to unprecedented progress toward hyperpolarization of molecules and opening onto molecular NMR [7]. At the same time, little attention has been paid to the cost and lifetime of hyperpolarization methods. These drawbacks limit the probability of further study on imaging and sensing of slower biological and chemical processes.

In the following, in order to find a relatively cheap and durable hyperpolarization method, this paper examines two advanced polarization techniques: dissolution dynamic nuclear polarization (d-DNP) as well as parahydrogen-induced polarization (PHIP). The approach is, by using a blended experimental and theoretical analysis, to compare the principle, cost, and limitations of two polarization technologies. The rest part of the paper is organized as follows. The second chapter starts focuses on the general principles and components of both d-DNP and PHIP techniques, whilst the third chapter draws attention to several applications in various fields. The fourth chapter then exhibits the theoretical and hardware limitations of the two methods, and finally, the fifth chapter concludes the paper with future outlooks.

## 2. Principles and components

### 2.1. Principles and components of d-DNP

The hardware conditions of the d-DNP and PHIP are shown in Fig. 1 [6]. The dissolution dynamic nuclear polarization is effective in enhancing the nuclear polarization of a substance. The d-DNP was invented by Ardenkjaer Larsen and his colleagues in 2003, whilst traditional DNP techniques can be traced back to the 1950s [8]. Today, there are two major commercial apparatuses of d-DNP: HyperSense and SPINlab polarizer. The former is manufactured by Oxford Instruments Ltd, whilst the latter originated from GE HealthCare [9]. The SPINlab DNP polarizer could be regenerated overnight with a sorption pump. The advantage of it is that it can operate at a temperature just below 1K and that it can handle several samples simultaneously [10].

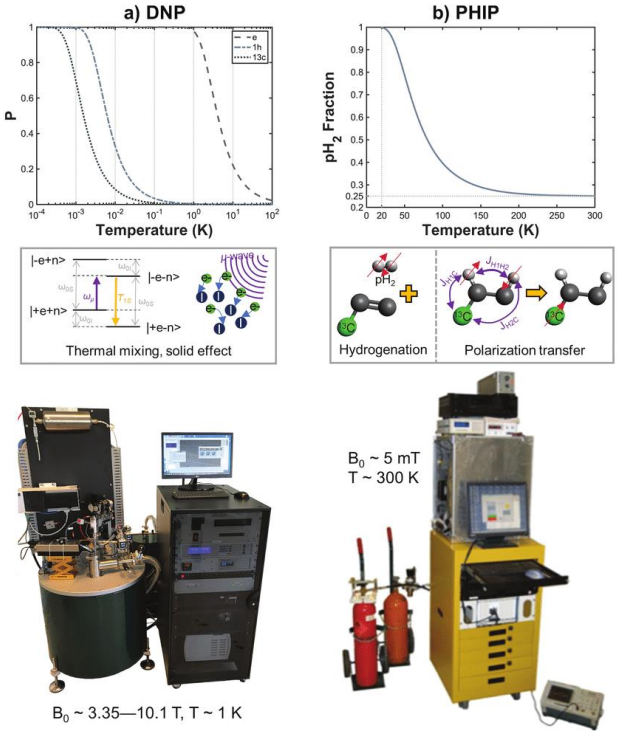


**Fig. 1** Hardware conditions of d-DNP and PHIP.

The d-DNP process requires a low temperature where there is a frozen glassy matrix, at which the tested sample is solid, followed by a sudden heat to a temperature of 1.5K. This rapid temperature rise is vital for increasing the signal strength of the nuclear spins, as the polarization rocketed. It ought to be noted that the tested sample is altered to the liquid state before a swift move to the MRI or NMR detecting device [11]. Typically, the d-DNP is performed in low magnetic fields, approximately at a magnetic field strength of 3.4T. Microwave irradiation is also required, at 94GHz or even higher. These conditions enable a large electron spin polarization and time-independent, spin-spin interaction through and enable further mechanisms, for instance, Solid Effect, Cross Effect, and Thermal Mixing [12]. A low temperature and relatively low magnetic field also ensure the establishment of a high thermal polarization of unpaired electron spins, and that there is minimum loss of nuclear polarization during the relaxation process.

D-DNP can be argued to be complex as the experimental apparatus is sophisticated, consisting of a cryostat, a microwave source, and a superconductive magnet. Additionally, as discussed, it is necessary to precisely control of temperature and the magnetic field strengt. The tested sample must be in a solid state, and the dissolution process is carried out with the guidance of a minute amount of boiling solvent, which triggers the dissolution process [13]. In general, a free radical molecule is used to be hyperpolarized and stimulated with 10-80mM of a polarizing agent (PA). The ultimate goal is to obtain a polarization transition from the PA to the nuclear spins of the molecules under test, then resulting in the dissolution of the tested sample, and hence transferred to either an MRI or NMR spectrometer. The detection process takes place at approximately room temperature. The d-DNP is a typical type of spin hyperpolarization, for which high non-thermal nuclear spin polarization is generated [11]. The MRI or NMR signal enhancement factor $\varepsilon^{\dagger}$ can be expressed with the equation

$$\varepsilon^{\dagger} = \frac{I_{DNP}}{I_{thermal}} = \varepsilon_{DNP} \frac{T_{detect}}{T_{DNP}} \frac{B_{DNP}}{B_{detect}} \tag{1}$$

Where $\varepsilon^{\dagger}$ is the enhancement of the MRI or NMR signal due to d-DNP executed at the temperature $T_{DNP}$. $T_{detect}$ is the temperature at which the MRI or NMR signal is then detected. D-DNP is carried out under the magnetic field strength $B_{DNP}$P, while $B_{detect}$ is the field strength under which the MRI or NMR signal is found. For instance, when the experiment is implemented at the temperature of 300K, and at 1.5K when the MRI signal is detected, whilst the initial magnetic field strength of 3.4T, and under a detected field strength of 9.4T, then the enhancement would be

$$\varepsilon^{\dagger} = 150 \frac{300K}{1.5K} \frac{3.4T}{9.4T} \approx 1.1 \times 10^4 \tag{2}$$

Through d-DNP, there is a dramatic jump in MRI sensitivity exceeding 10,000. Furthermore, the maximal enhancement of d-DNP may be expressed as

$$\varepsilon_{DNP} = \left|\frac{\gamma_e}{\gamma_n}\right| \tag{3}$$

$$\gamma_e = -\frac{g\mu_B}{\hbar} \tag{4}$$

Where $\gamma_e$ and $\gamma_n$ stand for the gyromagnetic constants of the unpaired electrons and the interacting nuclear spins, and the ratio between them gives the maximal enhancement of d-DNP. The second equation shows the equation for the gyromagnetic constant of unpaired electrons, for which $g$ is the Landé factor, $\mu_B$ is the Bohr magneton and $\hbar$ is the Planck constant divided by $2\pi$. Furthermore, the Hamiltonian of the whole target spin system may be calculated under the assumption of the harmonization of the external field with the nuclear spin of the target sample,

$$\mathcal{H} = 2\pi D S_z^2 + \gamma_e B_0 S_z + \sum_j \left[S \cdot A_j \cdot I_j - \gamma_n B_0 I_z^{(j)}\right] + \sum_{k>j} I_j \cdot B_{jk} \cdot I_k \tag{5}$$

In this case, $S_{x,y,z}$ are the Pauli spin matrix of the spin system of the tested sample; $\gamma_e$ and $\gamma_n$ are related to the gyromagnetic constants of nuclear spins interacting with the unpaired electrons; $I_{x,y,z}^{(j)}$ are the Pauli spin matrix of nuclear spin j; $A_j$, the hyperfine tensor, describes the spin-spin interaction between the sample and nuclear spin j, while $B_{jk}$ represents the magnetic dipole interaction between spins j and k. In addition to a glass transition temperature, a fortunate d-DNP experiment has to include a soluble, stable, and electron paramagnetic resonance (EPR) suited PA, for which the EPR's line shape, electron spin spectral diffusion rates, and electronic relaxation rates have a substantial amount of effect on the d-DNP process. The widely applied polarizing agents include tri-aryl-methyl and nitroxide radicals. Recent research focused on non-nitroxide radicals.

### 2.2. Principles and components of PHIP

The central reliance of PHIP is the internal spin order of parahydrogen. Together with orthohydrogen, parahydrogen is a nuclear spin isomer of hydrogen. In parahydrogen, the two proton spins are aligned antiparallel. The first applications of PHIP could be traced back to the 1980s [14]. Originally, scientists used the addition of parahydrogen to a double or triple bond of carbon, and hence intakes a highly polarized hydrogen atom into the molecule. Hydrogen atoms are known to have a short relaxation time, and therefore conduces to signal decay for up to a few seconds [15]. The latest research by Francesca Reineri and his colleagues in 2015 paid attention to side arm hydrogenation (SAH), in which parahydrogen acts as an ester sidearm added to a carboxyl $^{13}C$ moiety. Surprisingly, the addition of an arm side parahydrogen conducted to hyperpolarization of important metabolites such as 1-[$^{13}C$]-acetate, 1-[$^{13}C$]-pyruvate and 1-[$^{13}C$]-lactate [16].

In general, there are two most widely used approaches to PHIP: one with a Rh-based catalyst and the other with an organic solvent. The former carries out the addition of parahydrogen pairwise in an aqueous solution with the acceleration of a Co-based catalyst. The resulting product of d-DNP is suitable for animal studies. The only limitation of this method is that the removal of the catalyst is required to purify the resulting solution [17]. The latter dissolves the tested sample in an organic solvent, where the hyperpolarized sample is then transferred to an aqueous medium, and continued with the dissolution process. For this approach, there is no need for additional purification, and the targeted sample is directly produced with no catalysts [18].

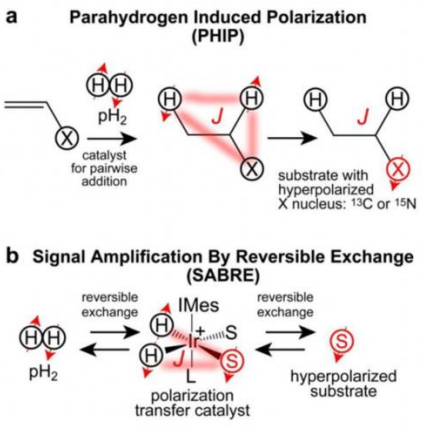


**Fig. 2** The sketch of PHIP and SABRE processes.

PHIP and its effects may be exhibited analytically. Despite the complexity of instruments, the model of a PHIP process is straightforward. Before any calculations, a concept has to be introduced, i.e., the 'hyperpolarized species'. This species refers to the imbalance between the concentrations of certain molecules in their respective spin states. For instance, $[H_2^*]$ is defined as an imbalance between parahydrogen and orthohydrogen concentrations

$$[H_2^*] = \frac{[H_2](4x_p - 1)}{3} \tag{6}$$

Where $[H_2]$ is the total hydrogen concentration in the tested sample, and $x_p$ is the fraction of concentration of parahydrogen. In this case, by conservation law, one mole of $[H_2^*]$ can be thoroughly transformed into one mole of $[P^*]$ (hyperpolarized product). The process of each d-DNP can be illustrated as

$$R + H_2^* \xrightarrow{\lambda \cdot K_{H_2}} P^*, P^* \xrightarrow{\frac{1}{T_1}} 0 \quad (7)$$

The hyperpolarized sample may disappear after a period of longitudinal relaxation.

The PHIP technique is showing extreme progress these years, due to the emergence of the non-hydrogenative Signal Amplification by Reversible Exchange (SABRE). This new approach includes a spin-spin coupling, which enables polarization transition from parahydrogen protons to the nucleus of the to-be-polarized sample. SABRE is particularly useful for long-lived hyperpolarized states (seen from Fig. 2) [6].

## 3. Applications

### 3.1. Applications of d-DNP

The applications of d-DNP are indeed numerous. D-DNP is creating huge impacts in the field of medical diagnostic imaging, especially with cancer diagnostics and treatment. For instance, hepatocellular carcinoma (HCC) is a typical entity that is often discovered at a late stage of cancers, conducing to over 780,000 deaths in 2018, according to the Global Cancer Observatory [19]. Currently, the most widely used d-DNP compound ought to be 1-C-13 pyruvate. By applying pyruvate d-DNP imaging, HCC can be detected with vague cell lines and extract images from the tumor tissues of HCC. Indeed, pyruvate is exceedingly suitable for metabolic imaging as it is the final product of glycolysis and has a relatively long relaxation time [20].

A recently discussed topic is to use of d-DNP to explore protein interactions, since d-DNP enhanced MRI or NMR may remove artifacts at physiological levels. D-DNP assisted NMR can be applied to visualize interactions and structural dynamics of protein molecules, and it is gaining mass attention in understanding intrinsically disordered proteins. Pyruvate has also been used to monitor metabolism in heart muscles and visualize infarcted regions. By using fast spectroscopic imaging, the current d-DNP techniques allow metabolic distribution maps to be detected and exhibited, which reinforces the ability to observe cancerous tissues in patients and hence guides further chemical treatment of the cancerous tissues [21].

### 3.2. Applications of PHIP

#### 3.2.1 Catalysis

PHIP is one of the most powerful techniques for MRI or NMR investigation of hydrogenation reactions and their catalytic mechanisms. There is broad use of metal-nanoparticles or other heterogeneous catalysts to generate PHIP gases (e.g., propene), credit to the fact that PHIP does not depend on expensive additional hardware and is relatively cost-efficient to implement in medical diagnostics [22]. PHIP is indeed an effective approach to investigating hydrogenation mechanisms and thus investigating homogeneous catalysis and catalytic intermediates.

#### 3.2.2 Peptides and amino acids

PHIP applications of peptides and amino acids are gradually attracting more attention. Employing PHIP peptides is becoming a marker in MRI and NMR studies. Peptides have profound impacts on the field of pharmacy. By inserting fluorenylmethyloxycarbonyl (fmoc) into the PHIP process, the NMR of peptides may be significantly enhanced [23].

# 4. Limitations

## 4.1. Limitations of d-DNP

Despite spectacular boosts in MRI and NMR signals, current d-DNP techniques are indeed complex, costly, and time-consuming. Contemporarily, the cost required for a complete d-DNP system is exceedingly high (several million US dollars). The variability of d-DNP experiments is certainly high, as there could be manual variables during sample preparation, dissolution, and detection. It is necessary to improve the hardware instruments and minimize the experimental strategies, in order to make it cheaper and easier to monitor [6]. With the generation of the high nuclear spin polarization during the d-DNP process, as well as the inevitable time period of sample dilution, the current technique does not allow consecutive experiments of d-NDP. Thus, the data collected is discrete, i.e., limited to the signal detected from a single excitation.

## 4.2. Limitations of PHIP

One limitation of the general PHIP technique is the requirement of additional pairwise parahydrogen to an unsaturated substrate. The invention of SABRE has solved this problem by forcing the tested sample to undergo a chemical exchange on a metal complex. Yet, this requirement of the metal complex as a catalyst is still unnecessary in the meantime. SABRE efficiency can still be improved. According to the fundamental principle of MRI, the signal intensity should rise while increasing the magnetic field strength of the experimental surroundings. Nevertheless, current studies show that even high magnetic field strengths cannot increase the polarization by more than an order of magnitude. The Boltzmann distribution of the spin populations has led to the short time span of PHIP-generated samples. The decays of samples, sometimes within seconds, exhibit a huge gap with the relaxation time, usually more than hours [24]. Consequently, future research requires effective methods for preserving nuclear spin information over longer time periods.

# 5. Conclusion

To sum up, it is demonstrated that both d-DNP and PHIP are constantly transforming and improving with new developments and discoveries. PHIP is particularly successful in enhancing MRI and NMR sensitivity, with a dramatic enhancement factor of greater than 10,000. Thus, the cost and time required for hyperpolarization processes are greatly reduced. In comparison, d-DNP is still needing further hardware development in order to simplify experimental strategies. D-DNP is facing technical and logical challenges like short signal lifetime and astronomical cost. These barriers force us to improve experiment setups to ensure future clinical usage. Whilst applications and studies of PHIP are relatively few in number when compared with d-DNP, new methods such as SABRE are demonstrating the extreme potential of PHIP. Current researches are showing the low-cost means of generating high nuclear spins and enhanced signals by PHIP. Besides, the most widespread polarization technique is still d-DNP, whilst PHIP is accessible to a few institutions across the globe.

In addition, the development of increasingly efficient catalysts is thriving. For instance, Rh-based catalysts and a variety of organic catalysts. With the improved filtering and diluting skills, product purity could be increased to another level. There is a bright view of the clinical applications of PHIP in various fields in the foreseeable future. In recent years, many studies showed improvements in PHIP field strength with the use of a non-Boltzmann population among spin energy levels [24]. The SABRE method of PHIP is indicating vast potential in molecular imaging probes. This approach undergoes polarization transfer by reversible exchange and the target sample remains chemically unchanged. In comparison to conventional PHIP, the SABRE technique is also illustrating new performances in biomedical applications. A very interesting field of future PHIP development is new detection mechanisms, e.g., atomic magnetometers or superconducting quantum interference devices. These apparatuses may lead to a huge boost in the concentration of detected spins, compared to traditional RF-detectors.

In conclusion, this research provides the general principles and applications of d-DNP and PHIP as two major polarization methods to enhance MRI and NMR sensitivity. Recent developments in hyperpolarization, including catalysis, hardware, transfer, and detection devices have paved the way for new applications of quantum polarization to magnetic resonance. It leads to more applications in physics, biochemistry, and medicine. Undoubtedly, with further improvements in theories and technology, hyperpolarization would be on a new stage in the foreseeable future.

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