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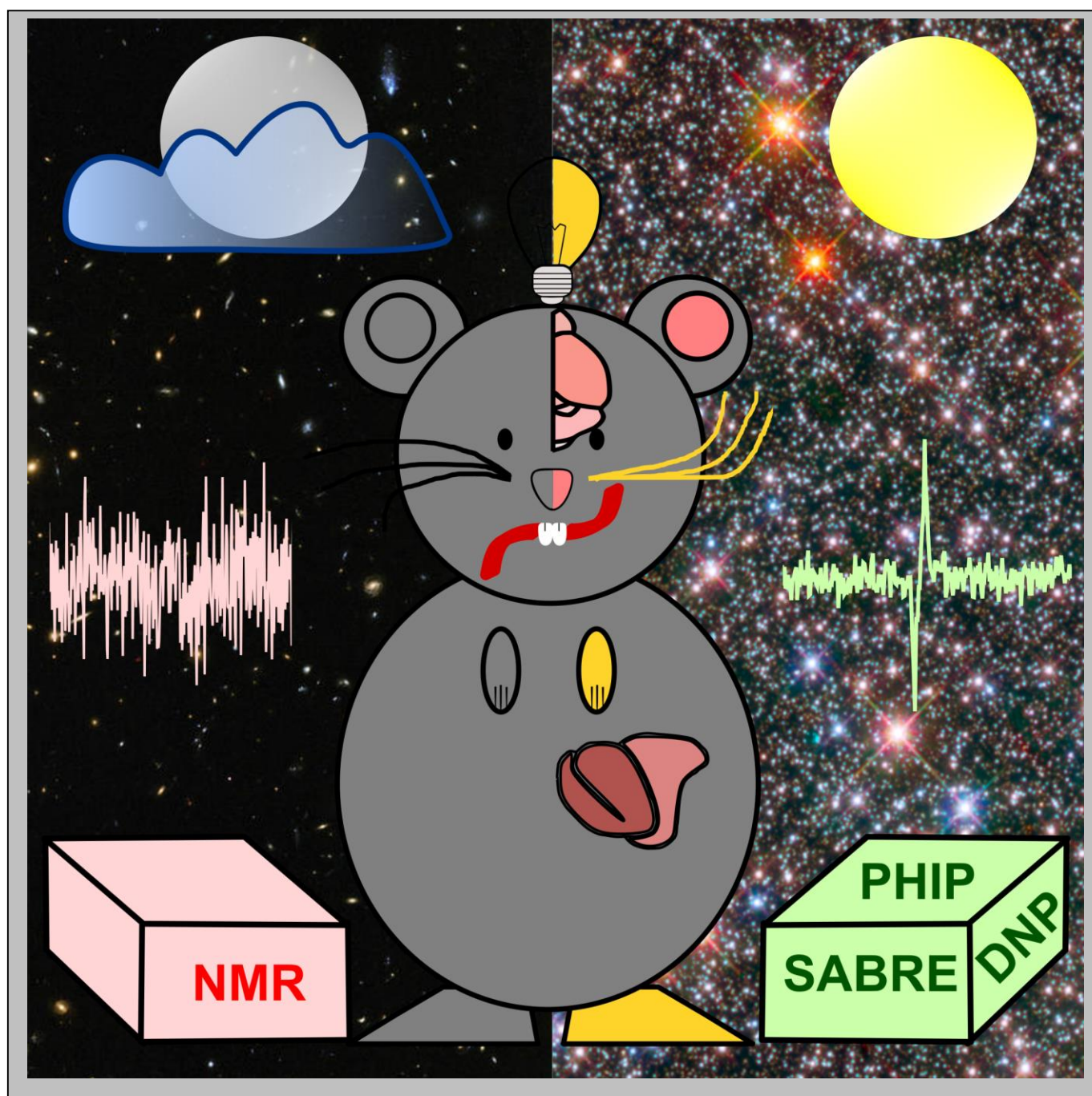
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Hyperpolarized NMR: *d*-DNP, PHIP, and SABRE

Kirill V. Kovtunov,^{*[a, b]} Ekaterina V. Pokochueva,^[a, b] Oleg G. Salnikov,^[a, b] Samuel Cousin,^[c] Dennis Kurzbach,^[d] Basile Vuichoud,^[c] Sami Jannin,^[c] Eduard Y. Chekmenev,^[e, f] Boyd M. Goodson,^[g] Danila A. Barskiy,^[h] and Igor V. Koptug^[a, b]



Abstract: NMR signals intensities can be enhanced by several orders of magnitude via utilization of techniques for hyperpolarization of different molecules, and it allows one to overcome the main sensitivity challenge of modern NMR/MRI techniques. Hyperpolarized fluids can be successfully used in different applications of material science and biomedicine. This focus review covers the fundamentals of the preparation of hyperpolarized liquids and gases via dissolution dynamic nuclear polarization (*d*-DNP) and parahydrogen-based techniques such as signal amplification by reversible exchange (SABRE) and parahydrogen-induced polarization (PHIP) in both heterogeneous and homogeneous processes. The different novel aspects of hyperpolarized fluids formation and utilization along with the possibility of NMR signal enhancement observation are described.

1. Dissolution dynamic nuclear polarization

Since its invention in 2003 by Ardenkjaer-Larsen and colleagues,^[1] dissolution dynamic nuclear polarization (*d*-DNP) has enabled exceptional sensitivity enhancements in the field of magnetic resonance (frequently greater than 10 000) and turned out to be a real game-changer for various applications including - among many others - *in-vivo* cancer detection, treatment-

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response monitoring,^[2,3] *in-cell* NMR^[4], drug development,^[5,6] and biomolecular analysis.^[7] *d*-DNP still undergoes significant developments and improvements. The aim of this review is to provide an overview of recent critical developments (Figure 1).

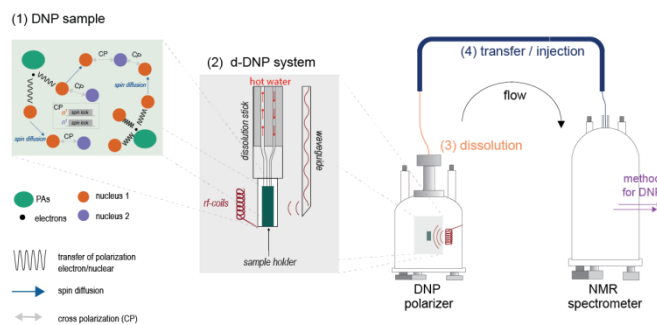


Figure 1. Schematic point of view of several key improvements implemented in *d*-DNP.

1.1. The general principle behind *d*-DNP

A *d*-DNP experiment starts with a specific sample preparation that in general uses a solution of one or several chemical compounds that are to be hyperpolarized doped with 10-80 mM of a polarizing agent (PA), generally a free radical molecule. The *d*-DNP solution is typically vitrified at low temperatures either *in-situ* within a dedicated DNP apparatus or prior to insertion into the latter. DNP setups provide i) a suitable magnetic field (typ. $B_{DNP} = 3.35 - 7$ T), with ii) low temperatures (typ. $T_{DNP} = 1.2 - 4.2$ K) to ensure a large electron spin polarization of the PAs, and iii) a possibility to irradiate a sample with a microwave (typ. $f_{\mu w} = 94$ GHz - 188 GHz and $P_{\mu w} \sim 100$ mW) resulting in the desired transfer of polarization from the PA to the nuclear spins of the target molecules, i.e., in dynamic nuclear polarization. The hyperpolarized sample is subsequently dissolved and rapidly transferred either to an MRI or NMR detection device to perform *d*-DNP enhanced experiments.^[1,8]

1.2. *d*-DNP sample formulation

The choice of PA is crucial for a successful *d*-DNP experiment (a list of popular PAs can be found in references ^[9-12]). The PA solubility, stability, and electron paramagnetic resonance (EPR) parameters are of great importance in DNP. Indeed, the EPR line shape, electronic relaxation rates, and electron spin spectral diffusion rates^[13] determine the efficiency of a given DNP mechanism such as the solid effect, the cross effect, or thermal mixing. The efficiency of a given mechanism often depends on the magnetic field and temperature. Different recent approaches towards a better understanding can be found in the works of Wenckebach,^[14] Vega^[15] and co-workers or Rosso and others^[16]. Two families of PAs are intensively used in *d*-DNP, namely nitroxide and tri-aryl-methyl (trityl) radicals, the former being especially effective for the polarization of nuclei with large gyromagnetic ratio (^1H), γ , and the latter for low- γ (^{13}C , ^{15}N , ^{31}P , ^6Li , ^{129}Xe , etc.) nuclei.

A high hyperpolarization uniformly distributed over the entire sample is generally achieved on efficiently vitrified samples capturing the spatial distribution of the PAs at the glass transition temperature T_g . Vitrification is typically achieved via the addition of a glassing agent such as glycerol. Recently it was found that such preparations can yet undergo ripening processes on the order of minutes that may influence the efficiency of DNP.^[17] The

PA concentration often needs to be finely optimized to maximize the hyperpolarization efficiency. However, one must beware of the fact that a too high PA concentration can have important effects on relaxation properties of a sample, especially after dissolution (*vide infra*) leading to exacerbated polarization losses. Nitroxide-based PAs can in principle be scavenged with vitamin C^[18] and trityl can be filtered through precipitation. More recently, alternative sample formulations involving *in-situ* UV-generated PAs^[19] or silica- and polymer-based hybrid polarizing solids (HYPSO^[20] and FLAP^[21]) have offered a way to solve this problem.

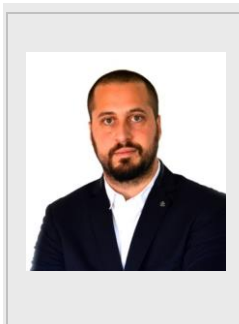
1.3. Polarization, dissolution and transfer

The polarization transfer from the PA's electron spins to nuclear spins of interest is in general induced by monochromatic or frequency modulated^[22] low-power microwave irradiation close to the central EPR transition. Cross-polarization (CP) pulse sequences have recently been coupled to *d*-DNP to boost performances in DNP of low- γ nuclei such as ¹³C or ¹⁵N by transferring the often higher and faster building ¹H

Basile Vuichoud was born in Lausanne (Switzerland) in 1988. He graduated from the Ecole Polytechnique Fédérale de Lausanne (EPFL) in 2013 with a Master in Molecular and Biological Chemistry and in 2017 with a PhD in Sciences, specialized in Nuclear Magnetic Resonance with Prof. Geoffrey Bodenhausen. He is currently working as a Post-doc in the group of Hyperpolarized Magnetic Resonance with Sami Jannin at the University of Claude Bernard Lyon 1 in France. His current researches are focused on various applications for dissolution Dynamic Nuclear Polarization coupled to NMR.



Sami Jannin received his PhD in Physics from the EPFL in Switzerland in 2009. Since then, his field of expertise has been centered around dissolution-DNP enhanced NMR. During 7 years he developed this research theme in the group of Geoffrey Bodenhausen, successively as a PostDoc and Bruker staff. In 2016, he was appointed full Professor at the Lyon University in France. His research interests are spanning from the development of new *d*-DNP methods and instrumentation, to the exploration of various *d*-DNP enhanced NMR applications in diverse fields such as analytical chemistry, drug discovery, or metabolomics



polarization to the latter. Polarization levels up to $P(^{13}\text{C}) \approx 70\%$ in ca. 20 min^[23,24] have been achieved. In *d*-DNP conditions, suspending (gating) the microwave irradiation during the CP contact can improve the efficiency.^[25]

Sample detection subsequent to hyperpolarization at low temperatures is achieved by dissolution with superheated (sometimes heavy) water and transfer to the NMR or MRI

apparatus. Two points need to be considered with respect to the survival of the hyperpolarized spin state during this procedure: i) dissolution and transfer need to be quicker than the involved nuclear relaxation processes, and ii) dilution of the PAs reduces the influence of paramagnetic relaxation enhancements (PREs).

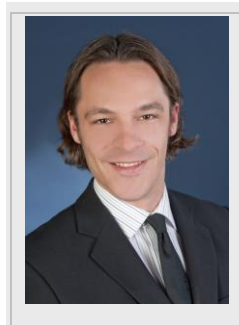
Though dilution of PAs is beneficial to the persistence of hyperpolarization, it does not always suffice to preserve the polarization during transfer. Instead, complete removal of the PAs is desirable. Depending on the sample formulation, this can be achieved by precipitation followed by filtration,^[26] phase separation,^[27,28] or a dilution-free freeze-melt approach.^[29]

Additionally, passages through low- or zero-field need to be avoided. To this end, a magnetic tunnel (sustaining a field of ca. 0.9 T) can be used^[30] which has, e.g., recently been used for efficient transfer of hyperpolarized water over distances > 5 m.^[31] Very recently, it has been demonstrated by Hilty and co-workers how the dissolution and transfer process can be coupled to electroporation of cell suspensions to enable in-cell *d*-DNP of arbitrary targets.^[32]

Samuel F. Cousin graduated from University of Paris (UPMC) and Ecole Normale Supérieure (ENS) in 2013 with a Master of Chemistry degree. He did his PhD under the supervision of Fabien Ferrage (ENS, France), and a first postdoc with Lucio Frydman (Weizmann Institute of Science, Israel). He is currently working as a postdoc in Sami Jannin laboratory (CRMN, Lyon).



Dennis Kurzbach received his PhD in chemistry at the Max Planck Institute for Polymer Research in 2013 focusing on EPR methods for the characterization of complex soft matter. Subsequently he moved to the University of Vienna developing integrative EPR and NMR approaches for intrinsically disordered proteins. Since 2015 he is coordinating the *d*-DNP team at the Ecole Normale Supérieure in Paris in the group of Geoffrey Bodenhausen investigating fundamental aspects and developing applications of the method to complex materials such as proteins as well as to multi-dimensional.



1.4. Robustness and repeatability

Though hyperpolarization can provide dramatic sensitivity enhancements exceeding 10 000, it can be of very limited use if robustness and repeatability are not guaranteed. This is in part due to the fact that several steps in the *d*-DNP process are manual (sample preparation, loading, dissolution) which are potential sources of variability. Nevertheless, a repeatability with a variation coefficient of 3.6% has been demonstrated recently on

a home-built instrument,^[33] which potentially opens the way to applications of dissolution DNP in fields such as quantitative metabolomics.

1.5. Toward transport to remote locations

As *d*-DNP experiments are quite complex, expert operators are often necessary. In this respect, it has been recently proposed that hyperpolarized substrates could be produced off-site and subsequently transported and dissolved directly on-site. In the liquid-state prolongation of hyperpolarization lifetimes can be achieved by, e.g., the conversion of hyperpolarization into long-lived states (LLS).^[34,35] Another route towards long-lived hyperpolarization in the solid-state consists in suppressing paramagnetic relaxation by the PAs by using non-persistent light-induced unpaired electrons.^[19] Alternatively, a heterogeneous sample formulation can be employed combined with spin diffusion relayed CP enhanced DNP.^[36] Hyperpolarization lifetimes as long as 37 h have been achieved via the latter strategy for [¹³C]sodium pyruvate.

d-DNP has become one of the most important hyperpolarization methods. It is still constantly transforming and improving with new methodological developments, enabling new applications in many areas of research. Yet, *d*-DNP experiments are often very expensive and remain restricted to a few groups world-wide, the most recent developments may pave the way to a more widespread applicability of *d*-DNP in the near future.

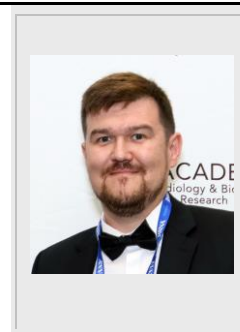
2. Homogeneous Parahydrogen-Induced Polarization

When parahydrogen—H₂ in its singlet state—is added in a pairwise manner to asymmetric unsaturated chemical compounds, the symmetry of the nascent hydrogen sites is broken, and it manifests itself as significantly enhanced nuclear spin polarization (also termed *hyperpolarization*). This effect was first demonstrated by Bowers and Weitekamp in the 1980s,^[37–39] and the acronym of parahydrogen induced polarization (PHIP)^[40,41] was later coined to describe the entire area of experiments when the resulting hyperpolarized (HP) state is produced by employing chemical transformation of parahydrogen (pH₂) gas. While PHIP was utilized for studies of chemical reactions in the first 15 years after its invention,^[41–43] it was not until the 2000s, when the teams of Goldman,^[44–47] Golman,^[48] and others^[49–51] pioneered approaches for intramolecular polarization transfer via spin-spin couplings from nascent parahydrogen protons to significantly longer-lived hyperpolarized ¹³C carboxyl sites (Figure 2a). Moreover, because the ¹³C *in vivo* background signal is low, HP ¹³C compounds were very quickly shown to be useful *in vivo* contrast agents in 2001.^[48,52–54] Homogeneous PHIP was also utilized for hyperpolarization of non-natural amino acids.^[55–57]

In the context of biomedical imaging applications, it is important that the resulting HP compound is injected as part of an aqueous medium. Two groups of approaches were developed over the years. In the first approach, the reaction of pH₂ pairwise addition is performed in the aqueous medium, which is facilitated by a water-soluble Rh-based catalyst.^[51,58] The catalyst has a low

toxicity profile,^[59] and the resulting HP solutions are suitable for studies in animal models.^[60,61] Future clinical translation would require an additional step of solution purification and removal of such metal-based catalysts. In the second approach, hydrogenation and polarization transfer is first accomplished in an organic solvent, and the HP compound is then extracted into an aqueous medium.^[62] The advantage of this approach is the production of pure (catalyst-free) solutions of HP compounds. Typical ¹³C T₁ of these HP contrast agents *in vivo* is in the range of 40–60 s.^[63] A number of biomedically relevant ¹³C HP contrast agents were developed. ¹³C HP 2-hydroxyethyl 1-[¹³C]-propionate (HEP) was shown to be a useful perfusion imaging agent.^[49] ¹³C HP 1-[¹³C]-succinate (SUC) and diethyl 1-[¹³C]-succinate (DES) were shown to be useful for probing TCA cycle metabolism.^[64–67] ¹³C HP tetrafluoropropyl 1-[¹³C]-propionate (TFPP)^[68] has been shown to be useful for probing vulnerable atherosclerotic plaques. ¹³C HP 1-[¹³C]-phospholactate^[69,70] (which metabolizes into 1-[¹³C]-lactate in blood^[71]) can be potentially useful for lactate imaging of cancer and heart diseases. In 2015, Reineri and co-workers pioneered PHIP by side arm hydrogenation (SAH),^[72,73] where pH₂ pairwise addition is accomplished into an ester side arm attached to a carboxyl ¹³C moiety. This approach significantly relieves the molecular requirements for unsaturated PHIP precursors. PHIP-SAH enabled hyperpolarization of key metabolites such as 1-[¹³C]-acetate,^[74] 1-[¹³C]-pyruvate,^[75] and 1-[¹³C]-lactate,^[76] and potentially will enable PHIP hyperpolarization of many other ¹³C-labeled metabolites. HP 1-[¹³C]-pyruvate is already at the stage of clinical trials using *d*-DNP.^[26] PHIP-SAH is of significantly lower cost (by approximately one order of magnitude) and is a significantly faster (by approximately one order of magnitude)^[77,78] alternative compared to *d*-DNP.^[1]

Prof. Eduard Y. Chekmenev, PhD in Physical Chemistry (supervisor Prof. Richard J. Wittebort) 2003, University of Louisville, KY, USA. Postdoctoral Fellow at NHMFL in Tallahassee, FL (Prof. Timothy Cross), Caltech (Prof. Daniel P. Weitekamp) and HMRI (Dr. Brian D. Ross). In 2009, Dr. Chekmenev started his hyperpolarization program at Vanderbilt University, and he was tenured in 2015. In 2018, he joined the faculty of Wayne State University and Karmanos Cancer Center as an Associate Professor. Research interests include development of methods of hyperpolarization and their biomedical and industrial uses.



A number of automated devices for the PHIP hyperpolarization process have been reported^[60,61,79–87] achieving ¹³C polarization up to 25%. Importantly, parahydrogen delivered polarization can be successfully transferred to other heteronuclei (¹⁵N^[88] and ¹⁹F^[89,90]).

3. Homogeneous Signal Amplification by Reversible Exchange

The key limitation of conventional PHIP is the requirement for a pairwise pH_2 addition to an unsaturated substrate. In 2009, Duckett and co-workers pioneered a non-hydrogenative Signal Amplification by Reversible Exchange (SABRE) technique.^[91–93] In this approach, parahydrogen and a to-be-hyperpolarized substrate molecule undergo simultaneous chemical exchange on a metal (typically Ir^[94]) complex. Spin order is transferred from pH_2 protons to a nucleus of the substrate via spin-spin couplings during the temporary formation of the complex shown in Figure 2b.

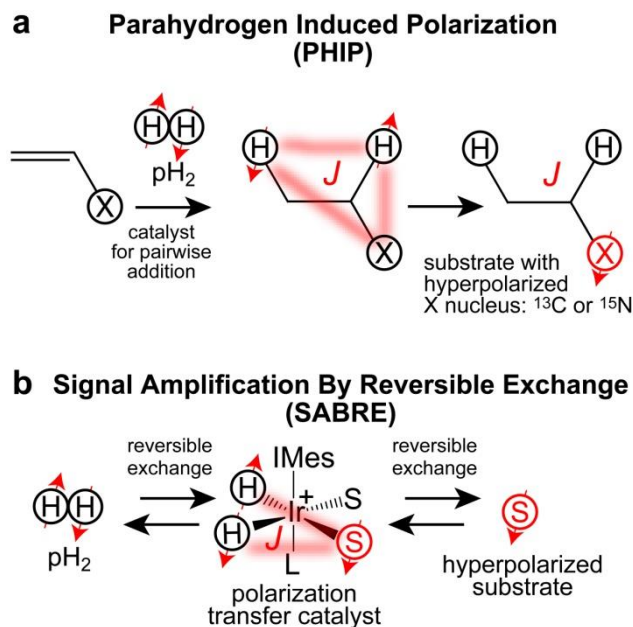


Figure 2. a) Schematic of the parahydrogen-induced polarization (PHIP) process. Note the symmetry breaking of the pH_2 singlet state in the first step of pairwise pH_2 addition. Spin-spin couplings (denoted as J) are employed for polarization transfer from nascent parahydrogen nuclear spins to an X nucleus (typically ^{13}C or ^{15}N). b) Schematic of the signal amplification by reversible exchange (SABRE) process. Note the simultaneous chemical exchange of pH_2 and the to-be-hyperpolarized substrate. Spin-spin couplings (denoted as J) enable polarization transfer.

Spontaneous polarization transfer occurs at a wide range of static magnetic fields. For example, the proton nuclei of a substrate are best polarized at magnetic fields of a few millitesla, when the magnetic field is matched to a combination of spin-spin couplings. On the other hand, Theis and co-workers have shown that microtesla magnetic fields provide matching conditions for polarization transfer to heteronuclei such as ^{15}N and ^{13}C .^[95–97] The list of amenable nuclei has been expanded to ^{31}P ,^[98] ^{29}Si , ^{19}F ^[99] and others.^[100] Spontaneous polarization transfer may also occur at high (Tesla) magnetic fields.^[101,102] Alternatively, radio frequency irradiation can be used to create level anti-crossings (LAC)^[103–105] for polarization transfer from parahydrogen to the to-be-hyperpolarized nuclei.^[106] Most SABRE experiments to date have been performed in organic solvents, although strategies for SABRE hyperpolarization in aqueous media have been demonstrated,^[107–113] which can potentially become suitable for *in*

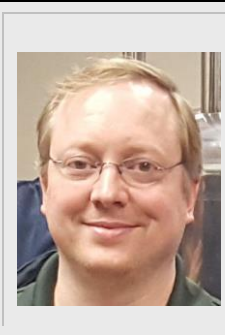
vivo experimentations. The latter would require Ir-based catalyst removal, e.g., by filtration.

^{13}C and ^{15}N sites are arguably the most interesting in the context of biomedical applications due to the ubiquitous occurrence of nitrogen and carbon atoms in biomolecules. ^{15}N T_1 values on the order of 3 minutes^[114,115] have been routinely demonstrated. Moreover, SABRE hyperpolarization is especially useful for preparation of HP long-lived spin states (LLSS),^[116,117] which have been shown to have relaxation constants up to 23 minutes^[116] – making the decay rate comparable to that of some radioactive-based contrast agents, e.g. the ^{11}C isotope. Polarization values of up to 50% have been demonstrated to date, with the entire hyperpolarization procedure requiring approximately 1 minute.^[118,119] No fully automated hyperpolarization equipment has been reported so far, although many setups have been described to date.^[120] A wide range of nitrogen-based heterocycles,^[96,114,121–123] diazirines,^[116] sulfur heterocyclic compounds^[124] and drugs^[125] have been hyperpolarized by SABRE technique, which can potentially become suitable molecular probes of hypoxia,^[115,118,126] pH sensing,^[127] and other processes^[128,129] *in vivo*, although no *in vivo* application has been demonstrated yet – largely because SABRE has been widely adopted only during the past few years.^[63]

4. Heterogeneous SABRE

One limitation of SABRE is the requirement of the catalyst to achieve the transfer of spin order from pH_2 to the target substrate. For many envisioned applications (including biomedical imaging), contamination of the hyperpolarized agent by the catalyst is prohibitive, necessitating some way to remove the catalyst while still enabling the agent to remain hyperpolarized for immediate use.

After graduating from Princeton (1995), **Boyd Goodson** earned his Ph.D. in 1999 with Alex Pines at UC Berkeley. Following a postdoc with Caltech's Ahmed Zewail, in 2002 Goodson joined SIU Carbondale, and was promoted to full professor in 2014. Recognitions include an NSF CAREER Award. His research concerns MR & optical spectroscopies and NMR/MRI sensitivity enhancement via hyperpolarization.



Recent work with Ir-based heterogeneous catalysts—where the catalyst moieties are covalently linked to solid supports—have demonstrated the feasibility of SABRE hyperpolarization under heterogeneous conditions (“HET-SABRE”). First, Shi *et al.* observed SABRE enhancements of 1H spins of pyridine with a variant of the Ir-IMes catalyst immobilized on microscale polymer supports functionalized with 4-dimethylaminopyridine.^[130] Although the initial enhancements were modest (~5-fold at 9.4 T), the heterogeneous origin of the SABRE effect was demonstrated. With the idea of improving SABRE efficiency by increasing the surface-area-to-volume ratio, the same group reported nanoscale

catalysts with Ir moieties immobilized on TiO₂/PMAA (poly(methacrylic acid)) and PVP (polyvinylpyridine) supports with core-shell and "comb" morphologies.^[131] These catalysts gave improved results, yielding ~7 and ~40-fold ¹H NMR enhancements at 9.4 T using PVP-based and TiO₂/PMAA-based catalysts, respectively. This work also demonstrated successful separation and re-use of heterogeneous catalysts. Very recently, Kovtunov *et al.* demonstrated an alternative synthesis to attach the Ir catalytic complexes to polymer-functionalized SiO₂ microbeads, and used these particles to show SABRE enhancement of heteronuclei under heterogeneous conditions.^[132] After administering p_{H2} gas under SABRE-SHEATH conditions (i.e., within a magnetic shield), enhancements of roughly ~100-fold were observed in the ¹⁵N NMR spectra of ¹⁵N-pyridine at 9.4 T (figure 3).

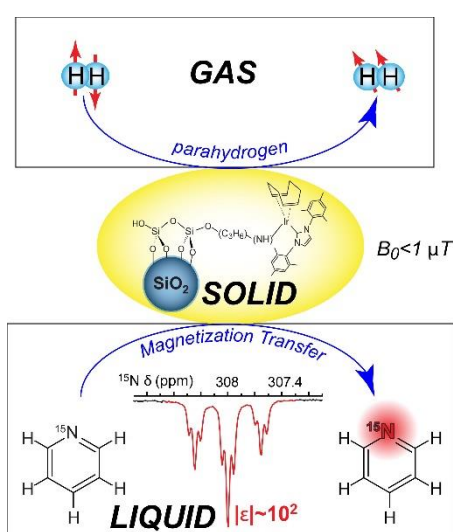


Figure 3. Bubbling p_{H2} into a solution containing a heterogeneous SABRE catalyst (immobilized on silica supports) yielded ~100-fold enhancement of ¹⁵N NMR of the ¹⁵N-pyridine substrate; bubbling was performed inside a magnetic shield (i.e. SABRE-SHEATH conditions). Adapted by permission from John Wiley and Sons, [120].

As an alternative approach for separating SABRE catalysts from HP substrates, Iali *et al.* recently achieved ~300-3000-fold enhancements using phase-transfer catalysis.^[133] In this method, a homogeneous SABRE catalyst is still used in an organic solvent. However, after the hyperpolarization step, the HP substrate is partitioned away from the catalyst into an immiscible aqueous phase.

5. Heterogeneous PHIP

The commonly used catalysts for heterogeneous hydrogenation and hydrogenolysis processes are nano-sized metal particles dispersed on porous oxide or carbon supports. It is widely accepted that dissociative hydrogen chemisorption takes place on such catalysts,^[134] and hydrogenation of unsaturated compounds occurs as a successive addition of two hydrogen atoms with intermediate formation of surface alkyl species.^[135–139] It is also

known that adsorbed hydrogen atoms can rapidly move over the surface of metal nanoparticles,^[140] embed into the crystal lattice of the metal,^[141–143] and migrate onto the support (also known as the spillover phenomenon).^[144] Therefore, a probability of pairwise addition of two hydrogen atoms from the same H₂ molecule to a substrate molecule should be extremely low. Furthermore, after dissociative chemisorption of H₂ molecule the adsorbed H atoms become magnetically inequivalent, leading to rapid loss of spin correlation between them.^[145] As a result, for a long time it was accepted that PHIP effects could not be observed in hydrogenation reactions over heterogeneous metal catalysts.

However, after successful demonstration of PHIP effects in hydrogenations catalyzed by immobilized metal complexes,^[146] it was found that PHIP can also be generated over supported metal catalysts. It was demonstrated that hyperpolarized propane is formed in the gas-phase hydrogenation of propene over Pt/Al₂O₃ and Pd/Al₂O₃.^[147] This observation indicates that the pairwise addition of hydrogen to unsaturated substrates over supported metal catalysts is possible. However, it should be noted that pairwise addition is not the main route of hydrogenation reactions over supported metal catalysts. For example, in the study mentioned above^[147] the contribution of the pairwise hydrogen addition route was found to be ca. 3%, although the actual value can be higher due to the partial loss of hyperpolarization as a result of relaxation process.

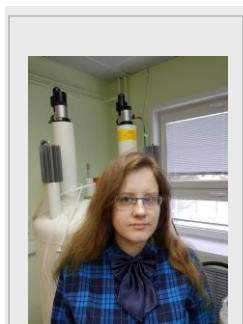
For a better understanding of factors affecting the pairwise addition over metal catalysts, systematic investigations were conducted. Zhivonitko *et al.*^[148] studied propene hydrogenation over platinum catalysts, supported on Al₂O₃, SiO₂, ZrO₂, and TiO₂. It was found that in the case of Pt/TiO₂ utilization the percentage of the pairwise addition was considerably higher and reached ca. 2.4%, while for other catalysts it was less than 1%. Such an increase was tentatively explained to be a result of low-temperature strong metal-support interactions (SMSI), which usually occur after high-temperature reduction of the metal catalysts on reducible supports, e.g. TiO₂, Nb₂O₅, CeO₂, and others.^[149,150]

Later, an analogous study of palladium catalysts supported on the same oxides was performed.^[151] The catalysts were tested in gas-phase hydrogenation of propyne and propene with parahydrogen.

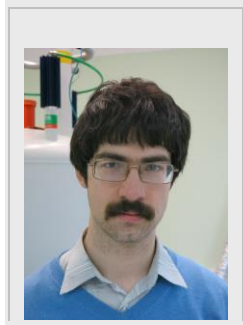
Dr. Kirill V. Kovtunov studied chemistry at the Novosibirsk State University, Russia. He completed a PhD in physical-chemistry in 2008 at the International Tomography Center under the supervision of Prof. Igor Koptiyug. His research interests include heterogeneous catalysis and utilization of PHIP techniques for NMR/MRI and mechanistic studies of heterogeneous reactions involving hydrogen. Currently he is the senior scientific researcher in the group of Prof. Igor Koptiyug.



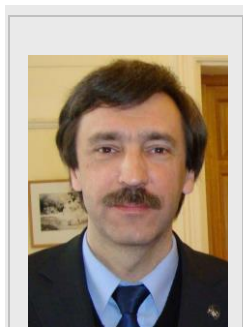
Ekaterina V. Pokochueva is an undergraduate student at Novosibirsk State University. Since 2017 she has been working on her diploma project at the International Tomography Center SB RAS in the group of Prof. Igor Koptuyug under the supervision of Dr. Kirill Kovtunov.



Oleg G. Salnikov completed his undergraduate studies in chemistry at Novosibirsk State University in 2014 and continued there as a PhD student. Since 2012 he has worked on HET-PHIP projects in the group of Prof. Igor Koptuyug under the supervision of Dr. Kirill Kovtunov. His research interests include the application of PHIP for mechanistic studies of heterogeneous catalytic reactions and the development of MR contrast agents using HET-PHIP.



Prof. Igor V. Koptuyug received his Ph.D. degree in 1991; in 1992–1995 he was a postdoctoral researcher in the photochemistry group of Professor N. J. Turro (Columbia University, New York). He earned his Dr. Sci. (Habilitation) degree in catalysis in 2003 and a title of Professor in 2006; currently, he is the deputy director of International Tomography Center, Siberian Branch of the Russian Academy of Sciences, Novosibirsk. His research interests include signal enhancement in NMR and applications of NMR and MRI in catalysis.



phase ^1H NMR due to nearly the same values of chemical shifts), and butane. In case of 1,3-butadiene and 1-butyne hydrogenation over $\text{Pt}/\text{Al}_2\text{O}_3$, Pt/SiO_2 , Pt/ZrO_2 , Pt/TiO_2 , and Pd/TiO_2 , PHIP effects were observed for all ^1H NMR signals of each reaction product (Figures 4 and 5).

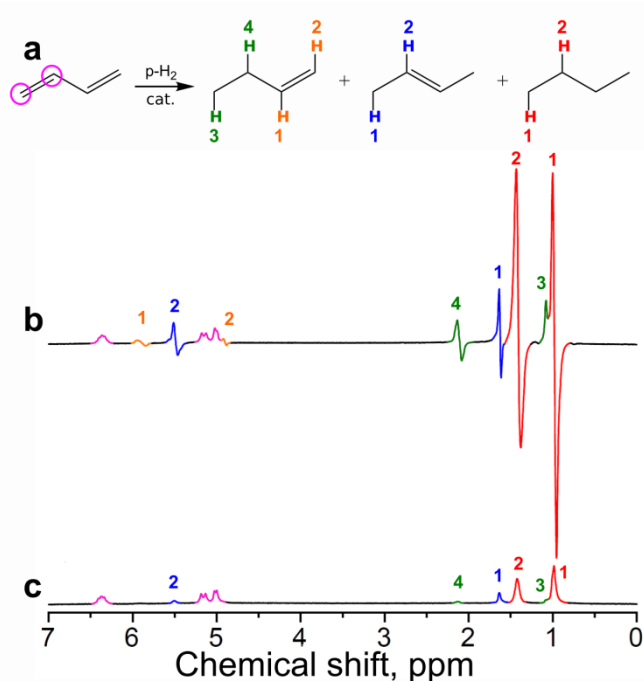
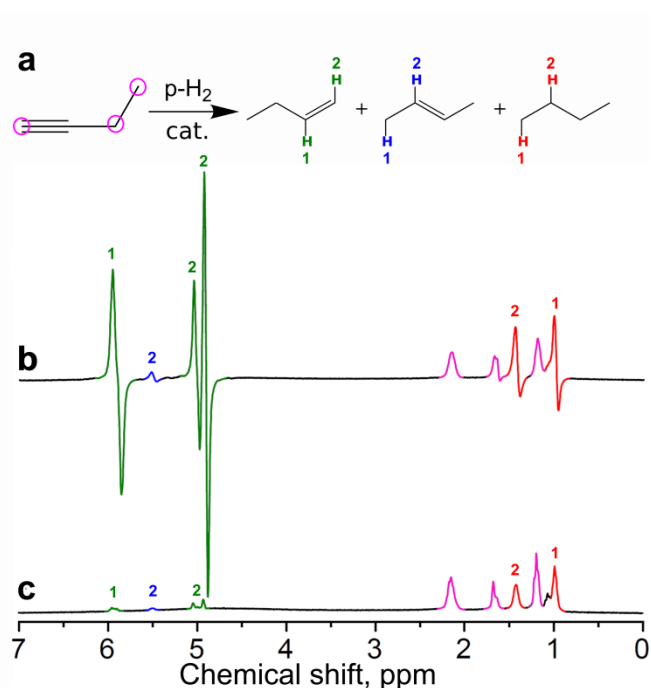


Figure 4. a) Reaction scheme of 1,3-butadiene hydrogenation. (b-c) ^1H NMR spectra acquired in hydrogenation of 1,3-butadiene over $\text{Pt}/\text{Al}_2\text{O}_3$ catalyst with b) parahydrogen and c) normal hydrogen. Adapted by permission from Springer Nature: Springer, *Top. Curr. Chem.* [133] © (2012).



When $\text{Pd}/\text{Al}_2\text{O}_3$, Pd/SiO_2 , or Pd/ZrO_2 were used in propyne hydrogenation, PHIP effects were observed only for the semi-hydrogenation product propene whereas propane protons did not exhibit hyperpolarization. At the same time, when Pd/TiO_2 was used in propyne hydrogenation, enhanced signals were observed for both propene and propane. Similar results were obtained in propene hydrogenation over Pd catalysts where only a Pd/TiO_2 catalyst was able to produce PHIP effects for propane.

The next step was the systematic study of the performance of Pt and Pd catalysts supported on Al_2O_3 , SiO_2 , ZrO_2 , or TiO_2 in hydrogenation of unsaturated C_4 hydrocarbons – 1,3-butadiene and 1-butyne.^[145] It was found that hydrogenation of both substrates results in formation of three products: 1-butene, 2-butene (its cis-trans isomers could not be distinguished by gas

Figure 5. a) Reaction scheme of 1-butyne hydrogenation. b-c) ^1H NMR spectra acquired in hydrogenation of 1-butyne over $\text{Pt}/\text{Al}_2\text{O}_3$ catalyst with (b) parahydrogen and (c) normal hydrogen. Adapted by permission from Springer Nature: Springer, Top. Curr. Chem. [133] © (2012).

Hyperpolarization of 1-butene protons labeled as 3 and 4 (Figure 4) and butane protons in 1,3-butadiene hydrogenation and 1-butene protons labeled as 1 and 2 (Figure 5) and butane protons in 1-butyne hydrogenation can be easily explained by pairwise addition of hydrogen to the corresponding unsaturated bonds. At the same time, observation of PHIP effects for other protons of 1-butene and 2-butene clearly indicates the occurrence of isomerization processes. Another interesting fact was the lack of hyperpolarization for 2-butene and butane in the case of 1,3-butadiene hydrogenation over $\text{Pd}/\text{Al}_2\text{O}_3$, Pd/SiO_2 , and Pd/ZrO_2 , whereas 1-butene exhibited PASADENA^[38] signals. At the same time PHIP effects were observed for all products of 1-butyne hydrogenation over these catalysts. Therefore, it can be concluded that the mechanism of hydrogenation reactions is strongly affected by the nature of both the active metal and the support, as well as by the nature of substrate.

Another interesting substrate for heterogeneous hydrogenation with parahydrogen is acetylene. The product of this reaction is ethylene, which in case of pairwise pH_2 addition is enriched with certain spin isomers.^[152] Such enrichment cannot be detected by NMR spectroscopy due to magnetic equivalence of hydrogen atoms in ethylene; however, if magnetic equivalence is broken, a direct NMR detection becomes possible. Zhivonitko *et al.* showed that it is possible to obtain a hyperpolarized adduct with distinctive antiphase signals in NMR spectra by addition of perfluoro(*para*-tolylsulfenyl)chloride to ethylene, which was produced by hydrogenation of acetylene with parahydrogen over Pd/TiO_2 .^[152] It was found that acetylene hydrogenation over palladium nanoparticles of different morphology (cubes, octahedra, cuboctahedra) can also yield C_4 -oligomeric products (1,3-butadiene, 1-butene, and 2-butene). Such oligomers exhibit high levels of polarization (up to 1.7%).^[153]

The range of substrates for producing PHIP effects is not limited to unsaturated hydrocarbons only. A successful hydrogenation of α,β -unsaturated carbonyl compounds over various supported catalysts,^[154] C_6 cyclic compounds,^[155] and furan derivatives^[156] over Rh/TiO_2 , Pd/TiO_2 , Pt/TiO_2 , and thiophene hydrodesulfurization over $\text{MoS}_2/\gamma\text{-Al}_2\text{O}_3$ and Pt/TiO_2 ^[157] with parahydrogen was performed. Such experiments can provide very useful mechanistic information about hydrogenation processes.

A promising class of heterogeneous catalysts for production of hyperpolarized compounds by PHIP are metal oxides, because the mobility of hydrogen atoms on the surface of oxides is significantly lower than on the metal surfaces—increasing the likelihood of pairwise H_2 addition. Indeed, in 2014 it was shown that pairwise addition of H_2 to unsaturated hydrocarbons (1,3-butadiene, 1-butyne, propyne) is possible over several oxide catalysts (CaO , Cr_2O_3 , CeO_2 , PtO_2 , PdO , and $\text{Pt}(\text{OH})_2$). However, the contribution of pairwise hydrogen addition route on such catalysts was comparable with the values for supported metal catalysts.^[158] In 2015–2016 Bowers *et al.* studied propene and propyne hydrogenation over CeO_2 nanocrystals of different shape (nanocubes, nano-octahedra, and nanorods).^[159] In the case of

propene hydrogenation, the percentage of pairwise hydrogen addition was 2.4% for all catalysts, i.e. no dependence on the nanocrystals shape was found. In contrast, in propyne hydrogenation strong influence of crystal shape was observed: for rods the percentage of the pairwise addition was 8.1%, whereas for octahedra it was only 1.6%.^[160]

Supported metal catalysts may produce PHIP effects not only in gas-phase, but also in liquid-phase hydrogenation. The first examples were hydrogenation of methyl propiolate over Pt/SiO_2 , Pd/SiO_2 , $\text{Pt}/\text{Al-MCM-48}$, $\text{Pt}/\text{Al-SBA-15}$, Rh/C , and hydrogenation of styrene and 1-phenyl-1-propyne over Pt/SiO_2 .^[161] In these experiments organic solvents were used (CD_3OD and CDCl_3). Later, PHIP effects were demonstrated in the aqueous phase hydrogenation of acrylamide over Rh/TiO_2 ^[162] yielding ^{13}C -hyperpolarized ethyl acetate with the achieved conversion of ca. 90%.^[163] and in the liquid-phase hydrogenation of propene performed by bubbling the propene-parahydrogen mixture through the Rh/TiO_2 or $\text{Rh}/\text{Al}_2\text{O}_3$ catalyst suspension in organic solvent (toluene- d_8 or acetone- d_6).^[162]

6. Heterogeneous MRI

The main advantage of the use of heterogeneous catalysts in the production of PHIP-hyperpolarized compounds is the possibility to easily separate the reaction product from the catalyst—just as with the case for SABRE, as mentioned in Section 4. Importantly, PHIP allows one to obtain a continuous flow of hyperpolarized gas, which can be used for MRI experiments. One of the most convenient gases is propane, because it is non-toxic (so it can be used for biomedical purposes) and can be easily produced in a hyperpolarized state by hydrogenation of propene with parahydrogen.^[164]

The first experiments of this kind were performed with the use of Wilkinson's catalyst immobilized on modified silica gel. It was demonstrated that hyperpolarized propane, produced by propene hydrogenation over heterogenized catalyst, could be successfully used for MR visualization of model objects (Figure 6)^[165] or catalytic microreactors in situ (Figure 7).^[166] However, such catalysts were found to be unstable under reaction conditions and the intensity of hyperpolarized signals was low due to the low catalytic activity.^[167,168]

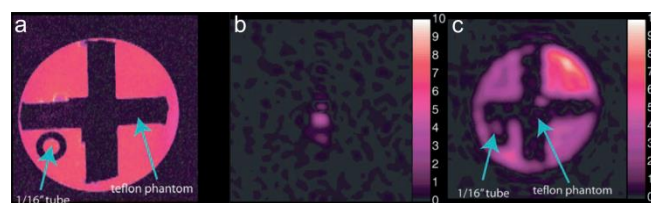


Figure 6. a) High-resolution ^1H MRI of a cross-shaped phantom filled with water. b) ^1H MRI of the same phantom filled with thermally polarized propene acquired by selective excitation of the protons of CH_2 group of propene. c) ^1H MRI of the same phantom filled with hyperpolarized propene acquired by selective excitation of the protons of CH_3 group of propane. Reproduced by permission from John Wiley and Sons, [153].

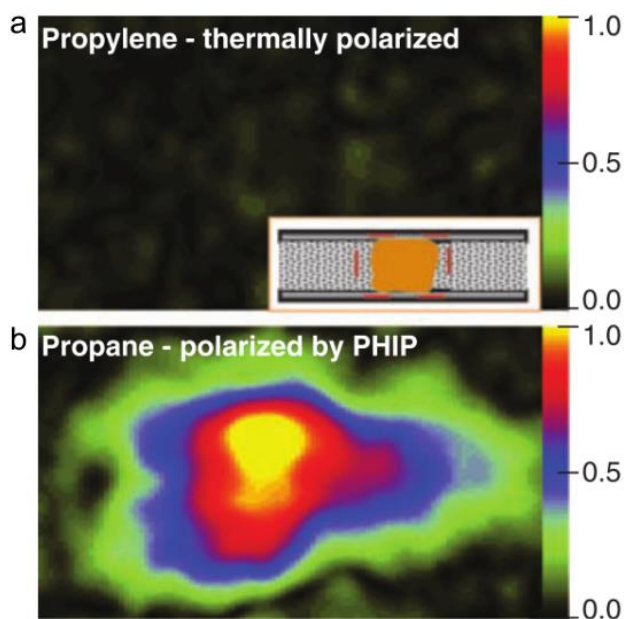


Figure 7. a) MRI of a tightly packed catalytic bed, filled with thermally polarized propene. b) MRI of the same area, filled with hyperpolarized propane. Reproduced by permission from The American Association for the Advancement of Science, [154].

In order to get a high-quality MR image, it is necessary to achieve a significant signal enhancement of the hyperpolarized product. Therefore, it is reasonable to use catalysts that provide both high percentage of pairwise addition of molecular hydrogen and high conversion of the reagents. In the study by Kovtunov *et al.*^[164] it was shown that among all metal catalysts supported on titanium dioxide, the best polarization levels are obtained with the use of Rh/TiO₂ catalyst with 1.6 nm particles. Despite the fact that maximum achieved percentage of polarization was 1.3%, such an enhancement was enough to perform 3D MRI of hyperpolarized propane (Figure 8).

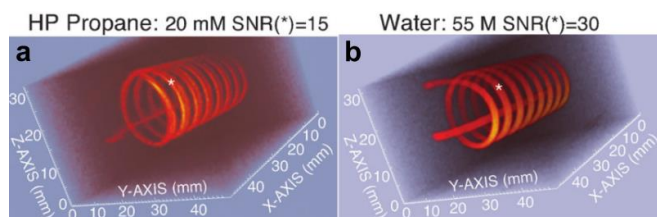


Figure 8. a) 3D gradient echo imaging of flowing hyperpolarized propane in a spiral phantom. b) Corresponding image of the same phantom filled with water. Reproduced by permission from John Wiley and Sons, [157].

The challenge in utilization of PHIP-hyperpolarized propane gas is the short lifetime of hyperpolarization (~ 0.6 s at Earth's magnetic field and within high-field MRI scanners). The possible solution is utilization of low magnetic fields in between these limits, e.g. 0.05 T, wherein the hyperpolarized propane relaxation time is ~ 4.7 s.^[169] The challenges of NMR and MRI detection of hyperpolarized propane at such magnetic fields may be overcome

by the use of spin-lock induced crossing (SLIC) pulse sequence,^[170] which allows one to convert the long-lived pseudo-singlet state of hyperpolarized propane into observable magnetization.^[169] Further increase in propane hyperpolarization lifetime can be gained by utilization of the deuterated substrate propene-d₆. For propene-d₆ produced by heterogeneous hydrogenation of propene-d₆ over Rh/TiO₂, ~ 6 s relaxation time at 0.05 T magnetic field was reported.^[171] The resultant gas can be successfully imaged at low magnetic field. Another promising approach for increasing hyperpolarized propane lifetime is the use of higher pressures. For example, at 7.6 atm hyperpolarized propane relaxation time is ~ 4.5 s at 9.4 T^[172] and ~ 13 s at 0.05 T.^[173]

An interesting approach is production of hyperpolarized propene from propyne, which would require the use of a selective catalyst. One of the suitable catalysts is the Pd-In/Al₂O₃ single-site catalyst.^[174] This catalyst demonstrated high selectivity to propene (up to 98%), as well as significant signal enhancement (ca. 3400-fold for CH-group of propene, corresponding to 9.4% polarization), while the conversion of propyne reached 18%. It allowed to acquire ¹H MRI of hyperpolarized propene (shown in Figure 9), which can be used in the future for development of MRI techniques for the in situ visualization of selective catalytic hydrogenations.

Therefore, heterogeneous PHIP can produce catalyst-free hyperpolarized molecules suitable for visualization via conventional MRI which, without doubt, opens up completely new areas of MRI applications in both the biomedical and the material science research areas.

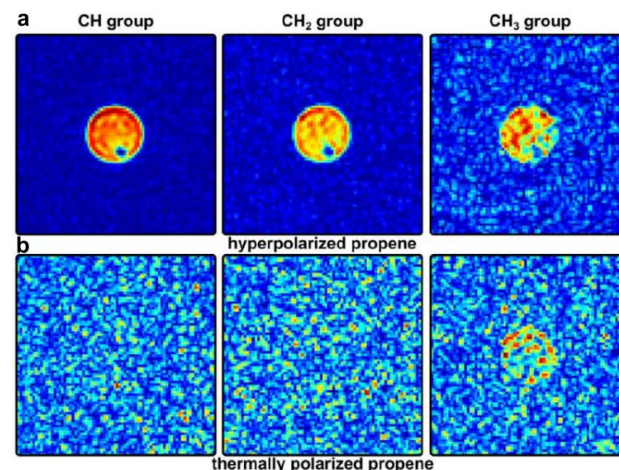


Figure 9. a) ¹H MRI of a 10 mm NMR tube filled with hyperpolarized propene acquired by selective excitation of the protons of CH- (left), CH₂- (middle), and CH₃- (right) groups of propene. b) Same as a, but with ¹H MRI obtained with thermally polarized propene corresponding protons. All images were acquired under gas-flow conditions. Matrix size and spatial resolution were 64 × 64 and 0.8 × 0.8 mm²/pixel respectively. Reproduced by permission from John Wiley and Sons, [162].

7. Analytical vision of SABRE and PHIP

7.1. Introduction

While major theoretical aspects of PHIP and SABRE (*i.e.*, magnetic field dependence and the efficiency of polarization transfer from ^1H to heteronuclei) are well understood, the polarization dependence on the chemical system parameters (such as reagents/products concentrations, reaction rate constants, *etc.*) still remain the subject of further study. Complete physicochemical models of the pH_2 -based hyperpolarization processes could significantly improve the polarization levels and yield of hyperpolarized contrast agents.

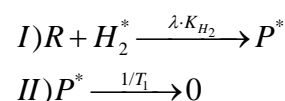
In principle, PHIP and SABRE allow transferring 100% of the spin order of pH_2 to a variety of heteronuclei in various chemical motifs.^[37,39] However, in practice the efficiency of the process is generally much lower than 100% and polarization levels on different substrates rarely achieves 20%.^[70,81,118] The net efficiency of the process is limited by several factors including reaction kinetics (*i.e.*, deviation of hydrogenation from the pairwise addition route), equilibration of *ortho/para* spin isomers of H_2 in the presence of metal complexes, low polarization transfer efficiency (from ^1H to heteronuclei) and relaxation/decoherence during the polarization build-up process.^[175,176] Here we briefly describe simple models which allow one to analyze factors that have the most dramatic effect on the final polarization levels in PHIP and SABRE processes. For the sake of brevity, we will mainly focus on homogeneous processes, while heterogeneous (HET) processes can be described similarly.

7.2. PHIP Modeling

PHIP is based on a hydrogenation reaction, *i.e.*, an addition of a hydrogen molecule (H_2) to a molecular precursor (R), a process that requires the presence of a catalyst. Homogeneous hydrogenation catalysts are typically platinum-group metal complexes in solution. While the detailed mechanism of homogeneous hydrogenation can be quite complex and may involve multiple short-lived intermediates, the end result is straightforward: formation of the reaction product (P).

It can be convenient to describe pH_2 -based polarization process by introducing concentrations of the so-called "hyperpolarized species".^[177] Concentrations of these "fictitious" species are defined as an imbalance between concentrations of molecules in the corresponding spin states. For example, a useful quantity is $[\text{H}_2^*]$, an imbalance between *para*- and *ortho*- H_2 concentrations, $[\text{H}_2^*] = [\text{H}_2](4x_p - 1)/3$, where $[\text{H}_2]$ is a total hydrogen concentration in solution and x_p is the pH_2 fraction. It can be shown that, in principle, one mole of $[\text{H}_2^*]$ can be completely converted into one mole of the hyperpolarized species $[\text{P}^*]$, described as the imbalance in concentration of product molecules in $|\beta\rangle$ and $|\alpha\rangle$ states: $[\text{P}^*] = [\text{P}_{|\beta\rangle}] - [\text{P}_{|\alpha\rangle}]$. Here $|\alpha\rangle$ and $|\beta\rangle$ are Zeeman states of the target to-be-polarized spin-1/2 nucleus in the product molecule, for example, ^{13}C .^[74]

Given these definitions, it is possible to write down the polarization build-up process in PHIP as the following chemical kinetic scheme:



The first process is the formation of hyperpolarized product P^* via pairwise hydrogenation of R by pH_2 . The second step describes how longitudinal relaxation leads to the disappearance of the hyperpolarized product. One should note that concentration of hyperpolarized species $[\text{P}^*]$ decays to zero if thermal polarization is neglected. Hydrogenation reaction kinetics is governed by a kinetic rate constant k_{H_2} . However, the polarization process also includes a quantity λ , the polarization transfer efficiency factor. This coefficient may include the magnetic field dependence of polarization transfer and the efficiency of pairwise hydrogen addition. Solving the above kinetic scheme by assuming first-order hydrogenation kinetics, one can obtain:

$$[\text{P}^*](t) = \lambda \left(\frac{4\chi_p - 1}{3} \right) \frac{k_{\text{H}_2} [\text{H}_2]_0}{1/T_1 - k_{\text{H}_2} [\text{R}]_0} \left(e^{-k_{\text{H}_2} [\text{R}]_0 t} - e^{-t/T_1} \right)$$

Here, $[\text{R}]_0$ and $[\text{H}_2]_0$ are the initial concentrations of the precursor and hydrogen in solution, respectively (here we assume that $[\text{R}]_0 \gg [\text{H}_2]_0$, which is readily achievable in closed vessels such as NMR tubes. Since the NMR signal of hyperpolarized species is enhanced by the factor η (defined as the maximal theoretical enhancement) compared to thermally polarized species, the attainable enhancement factor ε is derived as a ratio of concentrations of hyperpolarized species and thermally polarized species at any given moment in time:

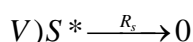
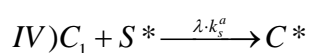
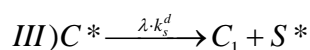
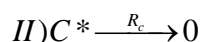
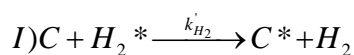
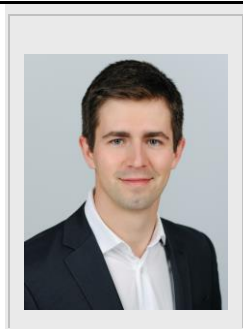
$$\varepsilon = \eta \frac{[\text{P}^*]}{[\text{P}]}$$

where the concentration $[\text{P}]$ is determined by the following equation: $[\text{P}](t) = [\text{H}_2]_0 (1 - e^{-k_{\text{H}_2} [\text{R}]_0 t})$. Emonds et al. conducted separate measurements of the reaction conversion, relaxation, and intensities of hyperpolarized signals under PASADENA conditions, and analyzed the results using the equations derived above.^[178] This analysis allowed them to accurately measure polarization transfer efficiency (λ) for a variety of hydrogenation catalysts at different magnetic fields. Surprisingly, not only concentration of reagents, but also ligand structure, *e.g.*, BINAP (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) vs. DPPB (1,4-bis(diphenylphosphino)butane) had a dramatic effect on λ . While λ for both catalysts $[\text{Rh}(\text{COD})\text{BINAP}]\text{BF}_4$ and $[\text{Rh}(\text{COD})\text{DPPB}]\text{BF}_4$ (COD=cyclooctadiene) was the same at the beginning of the hydrogenation reaction, λ in the case of DPPB started to decline after approximately 350 s, whereas the efficiency of BINAP continued to grow asymptotically toward reaching 0.4. The magnetic field of detection also affected the hyperpolarization process. When hydrogenation was performed at 14 T, the polarization transfer efficiency was 0.3 whereas λ measured at 7 T was only ~0.05. This observation clearly demonstrates that relaxation and *ortho/para*- H_2 equilibration in the intermediates prior to chemical reaction constitutes a highly relevant loss pathway. Overall, by modeling PHIP one can gain insights into reaction losses and optimize parameters to obtain higher polarization levels for the desired product.

7.3. SABRE Modeling

Modeling of the SABRE process can be realized in a manner similar to PHIP. However, the polarization build-up process is more complex and includes additional steps:

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The polarization build-up starts with the formation of hyperpolarized species C^* (i.e. the metal complex and parahydrogen; stage I), whose polarization decays with the relaxation rate constant $R_c = 1/T_1^c$ (stage II). This species takes part in the exchange process with the substrate governed by the substrate dissociation rate constant k_s^d (stage III) and substrate association rate constant k_s^a (stage IV). The hyperpolarized substrate concentration $[S^*]$ decays with a rate constant $R_s = 1/T_1^s$ (stage V). The parameter λ has a similar meaning as in PHIP, i.e., the efficiency of the polarization transfer process. In SABRE, this quantity depends on the NMR parameters of the system and the magnetic field in which the polarization process takes place. Analytical expressions for λ can be derived for both the high-field SABRE effect based on cross-relaxation^[101] and for conventional low-field SABRE (including SABRE-SHEATH)^[114] based on coherent redistribution of polarization in the complex.^[179] Solving the set of equations corresponding to the kinetic scheme written above, Barskiy et al. showed that the enhancement factor achievable in SABRE experiments can be written as follows:

$$\varepsilon = \eta \left(\frac{4\chi_p - 1}{3} \right) \frac{[C][H_2]}{[S]} \frac{\lambda \cdot k_s^d \cdot k_{H_2}}{R_s(\lambda \cdot k_s^d + R_c) + R_c \cdot \lambda \cdot k_s^d \frac{[C]}{[S]}}$$

This simple formula allows one to predict the dependence of SABRE enhancement on system parameters such as relaxation rates, reaction rate constants, J -couplings, etc. Remarkably, the formula not only correctly explains the trends observed in other studies (i.e., lower signal enhancements for higher substrate concentrations, linear dependence on the hydrogen supply rate, enhancement “saturation” with the increased catalyst concentration), but also it allows one to predict the optimal substrate dissociation rate which results in the maximal enhancement (given the known J -coupling topology of the polarization transfer complex). The analytical expression also shows that the key parameters of the system that should be optimized are the relaxation rates (especially, R_c) and not the dissociation rate constants. Partial deuteration of ligands and substrate molecules is a promising strategy to decrease R_c and R_s , particularly for maximizing 1H SABRE enhancements. Results presented by Rayner et al. confirm this statement by demonstrating several-fold NMR signal enhancement for partially deuterated substrates compared to non-deuterated analogues.^[119]

7.4. Modeling HET-PHIP/SABRE

Heterogeneous (HET) PHIP and SABRE processes can be described in a similar manner. For example, reaction of gaseous propylene with pH_2 over heterogeneous catalysts was characterized using a packed-bed reactor model at continuous flow at a fixed rate of flow.^[180] A combined analysis of spin dynamics and reaction kinetics allowed the authors to quantitatively explain the flow rate dependence of NMR signals of hyperpolarized propane in the ALTADENA (Adiabatic Longitudinal Transport After Dissociation Engenders Net Alignment)^[181] experiment. Remarkably, the main source of signal reduction in HET-PHIP is relaxation during the free flow in the gas phase and not relaxation of the hyperpolarized propane within the catalyst bed. Nonadiabaticity of the transfer (i.e., too high flow rates) can also reduce the observable signal. Therefore, optimal conditions exist in which a compensation between relaxation losses, adiabaticity of the gas flow, and reaction kinetics allow one to achieve maximal polarization on the molecules in the gas phase.

Therefore, attempts to provide theoretical descriptions of PHIP and SABRE phenomena are accompanied by difficulties of describing both nuclear spin dynamics and chemical kinetics (i.e., combination of coherent and incoherent processes). However, under certain conditions such descriptions are feasible and they can provide valuable information about mechanisms of polarization build-up processes that can be exploited to achieve improved results. Indeed, physicochemical modeling of pH_2 -based hyperpolarization is necessary for optimizing production capability and performance of contrast agents – the final goal that will enable these hyperpolarization techniques to become valuable tools in biomedicine.

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Keywords: parahydrogen • hyperpolarization • DNP • PHIP • SABRE

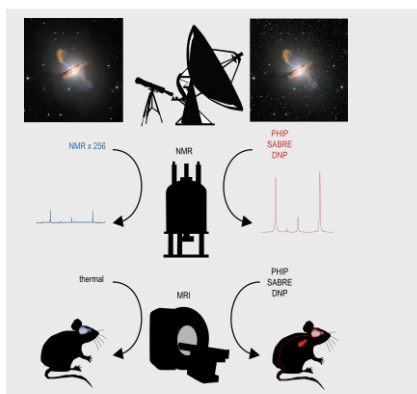
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FOCUS REVIEW

Dissolution dynamic nuclear polarization (α -DNP), signal amplification by reversible exchange (SABRE) and parahydrogen-induced polarization (PHIP) are shown to be very effective and promising approaches for the NMR signal enhancement and hyperpolarized contrast agents production.



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