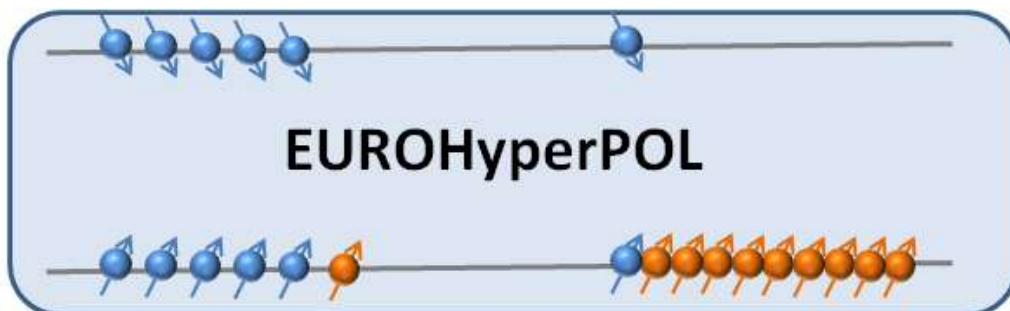


Annual Meeting of the MPNS COST Action TD 1103

**European Network for Hyperpolarization Physics and
Methodology in NMR and MRI**

ETH Zürich, Zürich, Switzerland, June 27-29 2014

Book of Abstracts



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We would like to sincerely thank all our sponsors for their generous support of the annual meeting. Without their contribution this meeting would not have been possible.

Program

Friday, 27.6.2014

08.00 - 08.45 Registration (HCI J floor)

08.45 - 09.00 Welcome and Opening (HCI J3)

09.00 - 10.30 Tutorial Talks (room HCI J3)

Boyd Goodson: Hyperpolarizing nuclear spins of noble gases via spin-exchange optical pumping: principles and practice for Enhancing NMR and MRI

Kerstin Münnemann: NMR and MRI sensitivity enhancement by Parahydrogen Induced Polarization

10.30 - 11.00 Coffee Break (HCI J floor)

11.00 - 12.30 Tutorial Talks (room HCI J3)

Sami Jannin: Dynamic Nuclear Polarization Appetizer

Malcolm H. Levitt: Long-Lived States

12.30 - 14.00 Lunch Break (Mensa)

14.00 - 15.00 Plenary Session (room HCI J3)

Jan Henrik Ardenkjær-Larsen: SpinLab-DNP polarizer designed with sterile use intent

Ville-Veikko Telkki: Metal-Free Catalysts for PHIP

15.00 - 15.30 Coffee Break (HCI J floor)

15.30 - 18.30 Working Group Meetings (HCI J3,4,6,7)

starting 18.30 Poster Session with Apéro (HCI J floor)

Saturday, 28.6.2014

09.00 - 10.00 Plenary Session (room HCI J3)

Thierry Brotin: ^{129}Xe @cryptophane complexes as new contrast agents for Magnetic Resonance Imaging

Robert Griffin: Overhauser Effects in Insulating Solids

10.00 - 10.30 Coffee Break (HCI J floor)

10.30 - 12.30 Working Group Meetings (HCI J3,4,6,7)

12.30 - 14.00 Lunch Break (Mensa)

14:00 - 14:30 Plenary Session (room HCI J3)

Jörg Wrachtrup: Sensing and polarization of small electron and nuclear spin clusters.

14.30 - 16.30 Working Group Meetings (HCI J3,4,6,7)

16.30 - 17.00 Coffee Break (HCI J floor)

17.00 - 19.00 Plenary Session (room HCI J3)

Reports from the Working Groups

Closing remarks

Sunday, 29.6.2014

10.00 - 13.00 closed Management-Committee Meeting

(ETH main building where Euromar will take place, room HG G19.1)

Talks in the Working Groups

The timings of the talks in the four working groups will be decided by the leaders of the working groups.

Working Group 1: Hardware and Instrumentation for Hyperpolarization (organised by Jean-Philippe Ansermet, Pierre-Jean Nacher, room HCI J3)

Marc Baldus: Dynamic Nuclear Polarization at 800 MHz/527 GHz

Danila A. Barskiy: Parahydrogen polarized propane: dependence on the reactant flow rate using heterogeneous catalyst and demonstration of fast high-resolution ^1H 3D MRI

Sean Bowen: Dissolution DNP: A multifaceted approach to optimization

Tian Cheng: A 140 GHz Corrugated Waveguide based on Stacked Rings Technology for Dissolution DNP

Vasyl Denysenkov: New double resonance structures for liquid state DNP at 400 MHz/260 GHz

Werner Heil: The benefits of long T_2^* : From fundamental physics to applied research

Jim Kempf: Brute-Force Hyperpolarization of 1- ^{13}C Pyruvic Acid

Daniel Lee: Sustainable Ultra-Low Temperatures for Magic Angle Spinning combined with Dynamic Nuclear Polarization

R. MacHattie: CPI Extended Interaction Klystron technology for DNP

Basile Vuichoud: Microwave Frequency Modulation to Enhance Dissolution Dynamic Nuclear Polarization

Anna Wojna-Pelczar: Novel ^{129}Xe SEOP polarizer for medical and material studies

Vladimir V. Zhivonitko: Microfluidic gas-flow imaging by parahydrogen-induced polarization and remote-detection NMR

Working Group 2/3: Theoretical Understanding of Hyperpolarization Strategies - Strategies to Minimise the Effect of Relaxation on Spin Hyperpolarization (organised by Konstantin Ivanov, Alberto Rosso, Hans-Martin Vieth, room HCI J7)

C.O. Bretschneider: Room-Temperature ^{13}C Hyperpolarization in NV-doped Diamonds: A Combined Laser and Microwave Irradiation Technique at Arbitrary Fields

Björn Corzilius: Paramagnet-Induced Signal Quenching and Relaxation in MAS DNP

M. Filibian: Temperature evolution of the electron-nucleus contact in pyruvic acid DNP

C. Griesinger: Sensitivity enhancement in solution by DNP and para- H_2

Y. Hovav: New Insights into the Role of the Electrons during DNP on Solids

Jan-Bernd Hövener: Recent Advances in Continuous Hyperpolarization using SABRE

G. Jeschke: The role of hyperfine coupling in solid-state electron-nuclear polarization transfer

A. Karabanov: Adiabatic elimination and stochastic unravelling in multi-spin quantum-mechanical simulations of DNP in solids

Nikita N. Lukzen: Manipulating spin hyper-polarization by means of adiabatic switching of a spin-locking RF-field

Markus Plaumann: PHIP Hyperpolarization of Fluorine: Applications, Examples and Problems

E.Ravera: Metal ions and DNP-considerations over the impact of electronic properties on DNP

D. Shimon: DNP on Heteronuclei: Theory and Experiments

M. Tessari: Sabre hyperpolarization at low concentrations

Working Group 4: Strategies to Maximise the Information that can be Acquired Using Hyperpolarized Spin Systems (organised by Lucio Frydman, Jim Wild, room HCI J4)

Sebastian Kozerke: Accelerating Hyperpolarized MRI by Exploiting Spatiotemporal Correlations and Sparsity

Christoffer Laustsen: Fast Padé Transform accelerated CSI for hyperpolarized MRS

P.-J. Nacher: Tests of RF phase encoding in low-field MRI

Madhwesha Rao: Spectroscopy of dissolved ^{129}Xe in human brain at 1.5 T

Neil J. Stewart: Human Lung MR Imaging using Naturally-Abundant ^{129}Xe with optimised 3D SSFP

G. Tastevin: Noise-triggered NMR maser bursts in HP liquid ^3He

Working Group 5: Synthetic Chemistry - Physics Interface in Hyperpolarization Methodology (organised by Patrick Berthault, Bela Bode, room HCI J6)

Ümit Akbey: Towards Higher Efficiency & Better Resolution in Dynamic Nuclear Polarization Enhanced Solid-State NMR

Jens Boss: Toward hyperpolarization of nuclear spins on diamond surfaces

Patrick Berthault: Ultrafast Z-Spectroscopy for Detection of ^{129}Xe NMR-Based Sensors

Björn Corzilius: The importance of polarizing agents and the chemical environment in MAS DNP

Olivier Lafon: Diffusion of polarizing agents into nanostructured materials: a critical factor for DNP-enhanced NMR experiments

Anil P. Jagtap: Increasing water-solubility of radicals for DNP using dendrimer chemistry

David Peat: Effects of field modulation on rate of growth of polarization at very high B_0/T

Miquel Pons: Polyradical species involving trityl radicals

M. Qi: Water soluble spacers for biradicals

Martin Schwarzwälder: Mesostructured Hybrid Silica Materials Characterization and Use as Polarization Matrices

Posters: (in alphabetical order of presenting author)

S. Ahola: Ultrafast multidimensional Laplace NMR

Aurélien Bernet: Cross-Polarization from ^1H to ^{13}C for Dissolution-DNP at 6.7 T and 1.2 K

C. Caspers: Tailoring 260 GHz-Gyrotron Radiation for DNP and ESR Applications

Sonia Colombo Serra: Interpreting DNP results of TEMPO doped samples by a rate equation approach in the TM regime

Nan Eshuis: SABRE Hyperpolarization in Trace Analysis

C. Glaubitz: High field Overhauser DNP Experiments on oriented fluid Lipid Bilayers using a Stripline/Fabry Perot Double Resonance Structure

D. Goldfarb: The ^{13}C solid DNP Mechanisms with Perchlorotriphenylmethyl Radicals – the Role of $^{35,37}\text{Cl}$

P. Haulte: DNP using photo-excited triplet states: above 70% proton spin polarization at moderate magnetic field and temperature

Julia Hollenbach: Use of hyperpolarized ^{129}Xe Nuclear Magnetic Resonance Spectroscopy for the analysis of modified diatomite

Konstantin L. Ivanov: Spin mixing at level anti-crossings in the rotating frame makes high-field SABRE feasible

Fabian Jähnig: The Haupt Effect for ^{12}C and ^{13}C Methyl Groups

Monu Kaushik: Investigation of the dynamic nuclear polarization transfer mechanism in molecular and crystalline model systems

Stephan Knecht: Explaining dynamic behavior of in situ SABRE by level anti crossing

Sami Emre Küçük: Liquid state DNP coupling constants for TEMPOL in acetone and DMSO from MD simulations

Grzegorz Kwiatkowski: Enhancing nuclear polarization of a nitrogen atom trapped inside a fullerene cage with ENDOR spectroscopy - comparison between experimental data and quantum-mechanical simulations

J.C. Lagomacini: Overhauser DNP efficiency of different nitroxide radicals at 9.4 T

Jiafei Mao: Host–Guest Complexes as Water-Soluble High-Performance DNP Polarizing Agents

Andriy Marko: Electron Spin-Spin Dipolar Interaction Role in High Field DNP Experiments on Liquid Radical Solutions

Leslie Mazuel: Hyperpolarized ^{13}C NMR spectroscopy: a new way to follow the glutamate-glutamine cycle in-vivo

Frederic Mentink-Vigier: Theory of Overhauser in Insulating Solids

M. Najdanova: Combining photo-CIDNP MAS NMR with strategies to determine structural dynamics in the photosynthetic process in natural reaction centers

A.K. Petukhov: ^3He Spin Exchange Optical Pumping with ultra-narrow band laser

Maria Theresia Pöschko: Proton spin noise from a hyperpolarized sample below 2K

Andrey N. Pravdivtsev: Level Anti-Crossings are a Key Factor for Understanding Magnetic Field Dependence of Hyperpolarization in SABRE Experiments

Madhwesha Rao: Dedicated receiver array coil for ^1H lung imaging with same-breath acquisition of hyperpolarized ^3He and ^{129}Xe gas

Oleg G. Salnikov: Investigation of mechanisms of heterogeneous hydrogenation α,β -unsaturated carbonyl compounds by parahydrogen-induced polarization (PHIP)

Manvendra Sharma: Rapid melt DNP

Michael Tayler: Uniting chromatography and NMR "on the strip"

S.G.J. van Meerten: Towards Overhauser DNP in supercritical CO_2

Basile Vuichoud: Indirect Measurement of Absolute Spin Polarization via Scalar-Coupled Spy Nuclei in Dissolution Dynamic Nuclear Polarization

Ralf Wunderlich: Optical Polarization of ^{13}C in Diamond via Nitrogen Vacancy Centers

Dongyoung Yoon: Dynamic nuclear polarization in the compensated semiconductor InP:Fe by optical pumping

Alexandra Yurkovskaya: Nuclear hyperpolarization allows to explore fine structural tuning of fast electron transfer in short lived oxidized peptides

J. Zill: Towards functional analysis of photosynthetic reaction centers of diatom *Stephanopyxis turris* with photo-CIDNP MAS NMR

Location

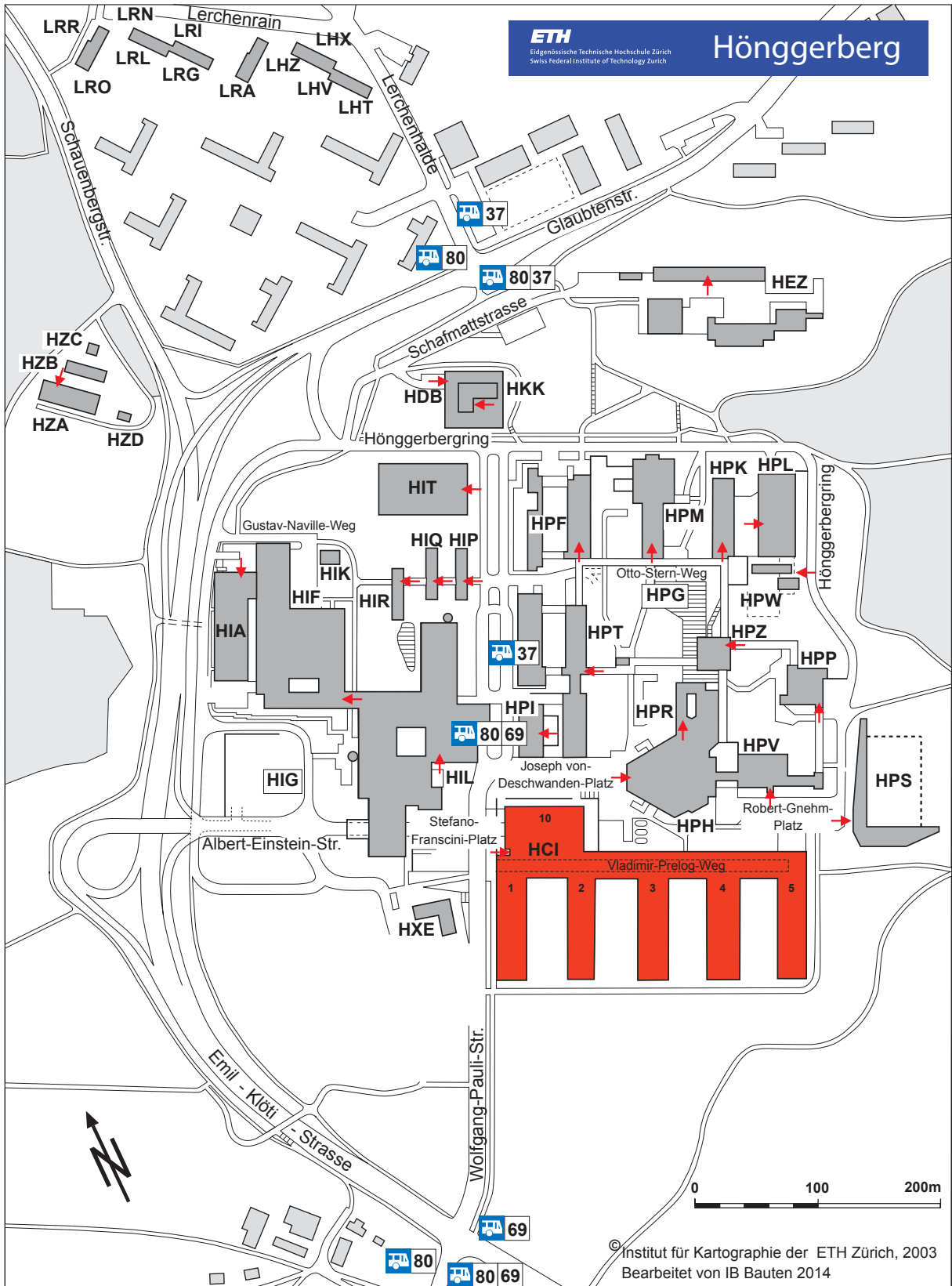
The scientific part of the meeting will be held at the Hoenggerberg campus of ETH (see <http://www.ethz.ch/en/campus/locations/zurich-region/hoenggerberg.html>) which is at the edge of the city. The talks will be in the Chemistry building HCI in the lecture halls HCI J3, HCI J4, HCI J6, and HCI J7. For a map of the Hoenggerberg campus see next page. The registration will also be in the HCI building on the J floor in front of the lecture halls. All plenary lectures will be in the lecture hall HCI J3.

To go to the Hoenggerberg, please take either tram no. 7 (direction Bahnhof Stettbach), 9 (direction Hirzenbach), 10 (direction Zurich Flughafen/airport), or no 14 (direction Seebach) from downtown to Milchbuck. At Milchbuck switch to bus 69 (direction ETH Hoenggerberg) to the terminal stop ETH Hoenggerberg. Do not get off at the stop Hoenggerberg which is located just outside of the campus. Alternatively, take either tram 11 (direction Auzelg) or tram 15 (direction Bucheggplatz) from any downtown location to Bucheggplatz. At Bucheggplatz switch to Bus 69 (direction ETH Hoenggerberg) to the terminal stop ETH Hoenggerberg. For detailed information see <http://www.zvv.ch/en>

The management-committee meeting on Sunday (only for members of the COST management committee) will be held at the central campus of ETH in the main building HG room G19.1. This is also where the EUROMAR conference will take place.

WIFI Access

WIFI access is available throughout the HCI building. You can either use the SSID "eduroam" if your institution participates in and authenticates eduroam access. In this case you have to use the username and password for your eduroam account. Or you can use the SSID "eth" or "eth5" using the conference username "cost2014" and the conference password "Euro+HyperPol".



Tutorial and Plenary Lectures

Hyperpolarizing nuclear spins of noble gases via spin-exchange optical pumping: principles and practice for Enhancing NMR and MRI

Boyd Goodson

*Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale,
IL 62901, USA*

Once limited to the realm of fundamental physics experiments, hyperpolarized (HP) noble gases have been exploited to enhance magnetic resonance signals for a wide range of applications, including: the imaging of lung space and other tissues in the human body; molecular imaging with xenon biosensors; probing cavities and surfaces of materials, molecules, and proteins; and low-field and remotely-detected NMR and MRI. In most cases, hyperpolarized noble gases are prepared by spin-exchange optical pumping (SEOP)—a two-step process by which angular momentum is transferred from circularly polarized laser photons first to the electronic spins of an alkali metal vapor, and then subsequently to the nuclear spins of the noble gas during collisions. Over time, high non-equilibrium spin order can accumulate in the nuclear spin degrees of freedom, corresponding to an orders-of-magnitude increase in nuclear spin polarization—and hence magnetic resonance sensitivity—for the gas. This tutorial lecture will focus on a number of key aspects governing the preparation and use of hyperpolarized noble gases for NMR and MRI. Following a brief introduction to the history of SEOP and its early application to magnetic resonance over two decades ago, topics will include: fundamental principles of SEOP; experimental aspects, methods, and instrumentation governing HP gas preparation; and “care and feeding” of HP gases to avoid premature loss of the hard-won but ultimately transient HP state. Particular attention will also be given to specific subjects of interest from my group’s laboratory as well as those of collaborators, including: stopped-flow SEOP; SEOP at the “extremes” of high xenon density and resonant photon flux; technological developments in high-power frequency-narrowed lasers; and the development of clinical-scale xenon “hyperpolarizers” capable of delivering near-unity ^{129}Xe polarization for human use.

NMR and MRI sensitivity enhancement by Parahydrogen Induced Polarization

Kerstin Münnemann

Max Planck Institute for Polymer Research, Mainz, Germany

Despite its wide applicability in chemistry, biology and medicine, Nuclear Magnetic Resonance (NMR) spectroscopy still suffers from its inherently low sensitivity. Exploiting the large signal enhancements associated with hyperpolarization techniques, such as Parahydrogen Induced Polarization (PHIP), however, NMR or MRI qualify for monitoring dynamic processes in real time.

PHIP is a way to achieve hyperpolarization of spin ensembles via a chemical route. The alignment of the nuclear spins in parahydrogen can be transferred to unsaturated molecules by a hydrogenation reaction resulting in dramatically enhanced NMR signals of the products [1]. Recently, it has been demonstrated that the spin order of the two parahydrogen atoms attached to a transition metal catalyst can be transferred to the ligand system of the catalyst. Chemical exchange with free ligand molecules in the solvent results in hyperpolarized dissolved molecules thereby overcoming the classical restriction of the PHIP technique to unsaturated molecules. This non-hydrogenative PHIP method is called Signal Amplification by Reversible Exchange (SABRE) [2].

This tutorial will give a brief introduction to the theoretical concepts involved in the hydrogenative and non-hydrogenative PHIP methods and present some interesting PHIP applications for NMR and MRI. Furthermore, the issue of the limited lifetime of the hyperpolarized state will be addressed and it will be discussed how the parahydrogen singlet state can be used to alleviate this shortcoming [3].

- [1] L. Buljubasich, M.B. Franzoni, K. Münnemann, "Parahydrogen Induced Polarization by Homogeneous Catalysis: Theory and Applications", *Topics in Current Chemistry*, **338**, 33 (2013).
- [2] R.W. Adams, J.A. Aguilar, K.D. Atkinson, M.J. Cowley, P.I. Elliott, S.B. Duckett, G.G. Green, I.G. Khazal, J. Lopez-Serrano, D.C. Williamson, "Reversible interactions with para-hydrogen enhance NMR sensitivity by polarization transfer", *Science* **323**, 1708 (2009).
- [3] M. B. Franzoni, L. Buljubasich, H. W. Spiess, K. Münnemann, "Long-Lived ^1H Singlet Spin States Originating from Para-Hydrogen in Cs-Symmetric Molecules Stored for Minutes in High Magnetic Fields", *J. Am. Chem. Soc.* **134**, 10393 (2012).

Dynamic Nuclear Polarization Appetizer

Sami Jannin

Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), Batochime, CH-1015 Lausanne, Switzerland ; Bruker BioSpin AG, Industriestrasse 26, 8117 Fällanden, Switzerland.

This tutorial lecture aims at introducing some basic concepts of dynamic nuclear polarization and illustrating how it is currently used as a tool for improving NMR sensitivity either in the solid- or in the liquid-state. A tentative outline of the talk is:

General introduction.

DNP mechanisms:

Overhauser DNP.

Solid Effect.

Cross Effect.

Thermal Mixing.

Experimental aspects of DNP and current research in:

Liquids.

Spinning solids.

Static solids.

Dissolved samples.

Concluding remarks and outlook.

Long-lived states

Malcolm H. Levitt

University of Southampton UK

In solution NMR, clusters of coupled nuclear spins may support states that have lifetimes much longer than the conventional spin-lattice relaxation time T_1 . In general, such states are called long-lived states (LLS): in the special case of spin-1/2 pairs, the LLS corresponds to singlet order (a population imbalance between the spin-zero singlet state, and the spin-1 triplet manifold). The phenomenon of LLS suggests many new possibilities in NMR and MRI, including the study of slow motional and chemical processes, and the transport of nuclear hyperpolarization. I will discuss some of the following topics:

- * the conditions under which long-lived states exist
- * how long-lived states are accessed
- * how long-lived states are maintained
- * relaxation mechanisms and theory of long-lived states
- * hyperpolarized long-lived states

SpinLab - DNP polarizer designed with sterile use intent

J. H. Ardenkjaer-Larsen

GE Healthcare, Park Alle 295, 2605 Broendby, Denmark.

SpinLab is a polarizer based on the dissolution-DNP method. The polarizer differs mainly from other polarizers in being designed with sterile use intent and being compatible with clinical use. The main features are: (1) an integral, disposable fluid path containing all pharmaceuticals and constituting the sterile barrier, (2) a closed-cycle cryogenic system designed to eliminate consumption of liquid cryogenes, (3) polarization of four parallel samples to increase throughput, (4) large sample polarization, (5) non-contact quality control of six parameters and (6) fully automated operation. The fluid path consists of a vial with the agent to be polarized, a pair of concentric inlet and outlet tubes connected to a syringe with dissolution medium and a receiver connected to the exit tube. The fluid path can operate to 400 K and 2.0 MPa, and can polarize sample sizes up to 2 mL. An inline filter removes the electron paramagnetic agent to less than 1 % in the case of [$1\text{-}^{13}\text{C}$]pyruvate. The system uses a sorption pump in conjunction with a cryocooler. A temperature of 0.8 K was achieved for 68 h (no sample heat loads) with a liquid helium volume of 2.4 L. The regeneration of the liquid helium could be achieved in less than 10 h, and the transition to cold (< 1.2 K) was achieved in less than 90 min. The loading of a sample adds less than 50 J of heat to the helium bath by introducing the sample over 15 min. The heat load imposed on the helium bath during dissolution was less than 70 J. The magnet field strength is 5 T with homogeneity of 50 ppm over a 35 mm DSV. The polarization after dissolution is typically above 50 %. The quality control system measures volume, temperature, pH, radical concentration, pyruvate concentration and polarization in about 10 s and the sample is delivered in a Medrad syringe for use with MR compatible power injector.

Metal-Free Catalysts for PHIP

Ville-Veikko Telkki,¹ Vladimir V. Zhivonitko,² Konstantin Chernichenko,³ Timo Repo,³
Markku Leskelä,³ Victor Sumerin³ and Igor V. Koptug²

¹*Department of Physics, NMR Research Group, University of Oulu, P.O. Box 3000, FIN-90014, Finland;* ²*Laboratory of Magnetic Resonance Microimaging, International Tomography Center SB RAS, Institutskaya St. 3A, 630090 Novosibirsk, Russia;* ³*Department of Chemistry, Laboratory of Inorganic Chemistry, University of Helsinki, P.O. Box 55, FIN-00014, Finland.*

So far parahydrogen-induced polarization (PHIP) has been based on the use of metal-containing hydrogenation catalysts. In this work, we demonstrate that metal-free compounds known as molecular tweezers can also produce PHIP. We show that ansa-aminoborane tweezers, called QCAT, provide (20-30)-fold signal enhancements of parahydrogen-originating hydrogens in ¹H NMR spectra, and the polarization can be transferred to ¹¹B nuclei. PHIP can be used for understanding the activation mechanism in metal-free catalytic systems. In this particular case, our results indicate that dihydrogen activation by QCAT and CAT tweezers is carried out in a pairwise manner. [1]

[1] V. V. Zhivonitko, V.-V. Telkki, K. Chernichenko, T. Repo, M. Leskelä, V. Sumerin, I. V. Koptug, *J. Am. Chem. Soc.* **132**, 598-601 (2014).

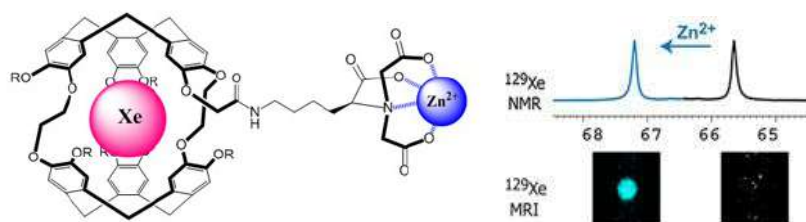
¹²⁹Xenon@cryptophane complexes as new contrast agents for Magnetic Resonance Imaging

Thierry Brotin

Laboratoire de Chimie de l'ENS LYON (UMR 5182 - CNRS), École Normale Supérieure de Lyon, 46 Allée d'Italie, 69364 Lyon, France,

Since the discovery of the high affinity of xenon for small cryptophane derivatives, the concept of cryptophane biosensors rapidly emerged in the early 2000's.¹ It is based on the use of the functionalized ¹²⁹Xenon@cryptophane complexes that can be potentially used as new Magnetic Resonance Imaging (MRI) contrast agents. This concept requires the use of molecular cages (cryptophanes) aimed at giving the encapsulated xenon a specific spectral signature and an optimized in-out xenon exchange.

We will discuss in this presentation some examples reported in the literature by our team and others. We will present the advantages and the drawbacks of this approach as well as the solutions that can be developed in the future to improve their use as efficient molecular biosensors for MRI imaging.



Example of a Xenon@cryptophane biosensor used for detection of Zn²⁺ cations. This approach enables detection of low concentration of Zn²⁺ ions in one xenon batch.

¹ Bartik, K. ; Luhmer, M. ; Dutasta, J.P. ; Collet, A. ; Reisse, J. *J. Am. Chem. Soc.* **1998**, 120, 784---791. Spence, M. M. ; Rubin, S. M. ; Dimitrov, I. E. ; Ruiz, E. J. ; Wemmer, D. E. ; Pines, A. ; Yao, S. Q. ; Tian, F. ; Schultz, P. G. *PNAS*, **2001**, 19, 10654---10657.

Overhauser Effects in Insulating Solids

R. G. Griffin

*Francis Bitter Magnet Laboratory and Department of Chemistry, Massachusetts
Institute of Technology, Cambridge, MA 02139, USA*

We report magic angle spinning (MAS), dynamic nuclear polarization (DNP) experiments at high magnetic fields (9.4 T and 14.1 T) using the narrow line polarizing agents BDPA dispersed in polystyrene, and sulfonated-BDPA and Trityl OX063 in glassy glycerol/water matrices. The ^1H DNP enhancement field profiles of the BDPA radicals exhibit a significant DNP Overhauser effect (OE) as well as a solid effect (SE) despite the fact that these samples are insulating solids, whereas trityl exhibits only a SE enhancement. In contrast to other DNP mechanisms such as the SE or CE, the experimental data suggest that the OE in non-conducting solids scales favorably with magnetic field, increasing in magnitude in going from 5 T, to 9.4 T and to 14.1 T. Simulations using a model two spin system consisting of an electron hyperfine coupled to a ^1H reproduce the essential features of the field profiles and indicate that the OE in these samples originates from the zero quantum (ZQ) cross relaxation induced by intramolecular delocalization of the unpaired electron and that the size of the hyperfine coupling is crucial to the magnitude of the enhancement. In ^1H -BDPA the OE is dominated by ZQ processes and is positive. In contrast, in ^2H -BDPA the double quantum (DQ) processes are dominant and yield a negative, albeit weak, enhancement as predicted by theory. Microwave field dependent studies show that the OE saturates at considerably lower power levels than the solid effect in the same samples. Our results provide new insights into the mechanism of the Overhauser effect, and also provide a new approach to perform DNP experiments at high magnetic fields.

Sensing and polarization of small electron and nuclear spin clusters

Jörg Wrachtrup

3rd Institute of Physics, Stuttgart University, Germany

Diamond defect centers provide a new means to detect weak NMR and EPR signals. The method relies on the intrinsic long relaxation time of diamond spins and their photophysics allowing for optical detection of the sensor signal, i.e. optically detected electron spin resonance. Sensing of the NMR signal of a few electron and nuclear spins has been demonstrated [1,2]. The strong optically induced electron spin alignment of the defect center electron spin can be transferred to surrounding electron and nuclear spins. The talk will describe recent advances in spin detection and hyperpolarization.

[1] Staudacher et al. Science 339 (2013) 561

[2] Steinert et al. Nature Comm. 4 (2013) 1651

Talks in Working Group 1

Hardware and Instrumentation for Hyperpolarization

Organized by

Jean-Philippe Ansermet, Pierre-Jean Nacher

Dynamic Nuclear Polarization at 800 MHz/527 GHz

Eline Koers, Deni Mance, Elwin van der Cruijssen, Mohammed Kaplan, Marc Baldus

*NMR Spectroscopy, Bijvoet Center for Biomolecular Research, Faculty of Science,
Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands*

Dynamic Nuclear Polarization (DNP) has become a powerful method to enhance spectroscopic sensitivity in the context of Magnetic Resonance Imaging (MRI) and Nuclear Magnetic Resonance (NMR) spectroscopy. We show that the combination of high field DNP (800 MHz/527 GHz) with Magic Angle Spinning (MAS) solid-state NMR can significantly enhance spectral resolution and allows exploitation of the paramagnetic relaxation properties of DNP polarizing agents as direct structural probes. Applied to a membrane-embedded potassium channel, this approach allowed us to refine the membrane-embedded channel structure and revealed conformational substates that are present during two different stages of the channel gating cycle. High-field DNP thus offers atomic insight into the role of molecular plasticity during the course of biomolecular function in a complex cellular environment.

Parahydrogen polarized propane: dependence on the reactant flow rate using heterogeneous catalyst and demonstration of fast high-resolution ^1H 3D MRI

Danila A. Barskiy^{a,b}, Oleg. G. Salnikov^{a,b}, Kirill V. Kovtunov^a, Igor V. Koptug^{a,b}, Milton L. Truong^c, Aaron M. Coffey^c, Eduard Y. Chekmenev^{c,d}

a - International Tomography Center, Novosibirsk, Russia; b - Novosibirsk State University, Novosibirsk, Russia; c - Institute of Imaging Science, Nashville, United States; d - Vanderbilt University, Nashville, United States

Parahydrogen-induced polarization (PHIP) of nuclear spins can dramatically enhance NMR signals [1]. If singlet nuclear spin order of parahydrogen survives during the catalytic hydrogenation of molecular precursor, the ensemble of reaction product molecules appears in the state with non-equilibrium population of spin energy levels. Recently, PHIP techniques progressed to biomedical applications by applying heterogeneous (HET) instead of homogeneous catalytic systems for hyperpolarization (HP) production [2]. HET PHIP can produce gaseous non-toxic HP molecular contrast agents, such as propane, in continuous mode with direct ^1H MRI signal read-out [3].

In the present work, we describe the analysis of propane PHIP formed by reaction of gaseous propylene with parahydrogen over Rh/TiO₂ catalyst at different reactant flow rates. Optimum reactants' flow rate for propane hyperpolarization is demonstrated: i.e. higher flow rates lead to non-adiabatic transfer of propane to the high magnetic field of NMR spectrometer, while lower flow rates lead to significant loss of polarization intensity due to the efficient magnetization relaxation of hydrogenated product on the catalyst bed and during gas transportation.

^1H 3D MRI of HP propane was demonstrated using the optimal flow rate conditions. High proton HP ($\%P_{\text{H}} = 1.3\%$) per each hyperpolarized proton enabled micro-scale spatial resolution ($625 \times 625 \times 625 \mu\text{m}^3$) and large imaging matrix ($128 \times 128 \times 32$) using pre-clinical 4.7 T MRI scanner with total scan time of 17.4 s. 3D MRI of propane potentially enables imaging applications in porous media, human lungs, etc. without isotopic enrichment of hyperpolarized contrast media and using relatively simple hyperpolarization setup and conventional proton MRI hardware in contrast to hyperpolarized heteronuclei, e.g. ^{129}Xe , ^{83}Kr , ^3He , and others.

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Dissolution DNP: A multifaceted approach to optimization

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Dissolution DNP poses unique challenges due to the transition between the solid state and the solution state. While significant effort has been applied to attaining the highest polarization levels in the solid state, it is important that this translates into the highest possible signal in the solution state after dissolution. To accomplish this, it is necessary to optimize both the dissolution hardware as well as the sample formulations.

In terms of hardware, we have designed a dissolution system which permits the use of large solvent volumes while permitting independent control of temperature and pressure. This is coupled with a dissolution head equipped with a nozzle to focus incoming solvent onto the frozen sample. This encourages efficient mixing for rapid dissolution. Additionally, large diameter tubing is employed to reduce the pressure drop and make the dissolution process more rapid. We have also implemented an optical absorbance based setup to measure the sample concentration profile in real time.

To maximize the available signal, it is necessary for samples to be both highly concentrated and capable of attaining high levels of polarization. We have devised new sample formulations that meet both of these objectives with the additional benefits of being stable and having favorable dissolution properties. Post-dissolution properties are also of fundamental importance and we have developed several strategies for both sample dissolution as well as post-dissolution techniques such as rapid chromatography.

Through the combination of improved hardware, better sample formulations, and novel post-dissolution analytical techniques; it is possible to better preserve the high levels of polarization achieved in the solid state until the point of measurement in the liquid state. These advances serve to further increase the applicability of dissolution-DNP to new systems and modalities where it was previously less well-suited.

A 140 GHz Corrugated Waveguide based on Stacked Rings Technology for Dissolution DNP

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Most of the reported high-field DNP studies showed a common issue related to the relatively high power need to reach maximum nuclear spin polarization [1-3]. In the present study we compare the performance of a corrugated waveguide based on the stacked rings technology [4-5] and designed for dissolution DNP at 140 GHz with the performance of a conventional smooth-wall circular waveguide for polarizing ¹³C spins in a 5T dissolution polarizer [6-7]. The 32% transmission power loss measured with the smooth-wall circular waveguide was reduced to 10% with the corrugated waveguide. The ¹³C solid-state NMR signal enhancement obtained in a 3M [1-¹³C] acetate sample doped with 50mM TEMPOL reached 127±8 at 4 K using corrugated waveguide. At 1.6 K, an enhancement factor of 200±11 was measured, which corresponds to a ¹³C polarization of 16.8%. In addition to a gain in ¹³C solid-state polarization, we also observed that the polarization build-up time constant was about 45% shorter at 1.6 K.

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New double resonance structures for liquid state DNP at 400 MHz/260 GHz

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Recently achieved DNP enhancements in liquids at high magnetic fields [1-5] have initiated strong interest in possible applications of the method. However, spectral resolution of available DNP probes was strongly limited due to the complicated geometry mostly determined by microwave components involved in the design of the probes [1]. Additionally the sample size is very small in the used fundamental mode MW resonant structures. Together with a low RF filling factor this resulted in reduced NMR signal amplitude, hampering overall sensitivity gain by Overhauser DNP at high magnetic fields.

Here we present new double resonance structures [6] for liquid-state DNP at 9.4 T (260 GHz/ 400 MHz) that offer improved spectral resolution (5 Hz ¹H NMR line in water), micro-fluidic sample handling with a typical sample volume of 100 nl and active sample cooling to compensate for MW heating of the sample under EPR excitation. All together significant improved NMR sensitivity with respect to our 9.2 T DNP probes designed previously have been achieved. First applications will be shown to demonstrate the performance and possibilities of these new probes.

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The benefits of long T_2^* : From fundamental physics to applied research

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Hyperpolarized (HP) noble gases like ^3He and ^{129}Xe show long T_2^* relaxation times which can reach more than 100 h at low magnetic fields and in the regime of motional narrowing. The talk discusses the benefits of long spin coherence times. The method is based on the detection of free precession of the nuclear spins by means of standard NMR techniques or by using SQUIDs as low-noise magnetic flux detectors. At low magnetic fields ($B \sim 1 \mu\text{T}$) the detection of the free precession of co-located $^3\text{He}/^{129}\text{Xe}$ nuclear spins (clock comparison) is used as ultra-sensitive probe for non-magnetic spin interactions like Lorentz violating interactions, etc., since the magnetic dipole interaction (Zeeman-term) drops out in the weighted frequency difference, i.e., $\Delta\omega = \omega_{\text{He}} - \gamma_{\text{He}} / \gamma_{\text{Xe}} \cdot \omega_{\text{Xe}}$ of the respective Larmor frequencies. At high magnetic fields $B > 1$ Tesla, HP ^3He still reaches a T_2^* of several minutes and can be used as highly sensitive magnetometer which reaches a relative precision of $\Delta B/B < 10^{-12}$.

Brute-Force Hyperpolarization of 1-¹³C Pyruvic Acid

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We demonstrate a new approach to hyperpolarization (HP), achieving 1500-fold ¹³C enhancement with 1-¹³C pyruvic acid. Brute-force HP polarizes molecules with high B field and ultralow T , without resorting to microwaves or co-dispersed radicals. The latter simplifies the pharmacy and quality assurance processes prior to human imaging and avoids radical-induced T_1 losses. It also enables scalable production by avoiding confinement of the sample within a microwave field.

Critically, we have shown that a molecule polarized in high B/T (e.g., 14 T and 500 mK) can be extracted in the *solid state*. That opens new possibilities for the *transport* of slowly relaxing ¹³C HP from production sites to imaging centers. A key milestone here is the crossing of the 'valley of death' (a profile of T_1 vs T with minimum <1 s in the solid state) with no more than 30% loss of the starting polarization. We do this by pneumatically ejecting a sample from the polarizing cryostat, collecting it in a modest 2T permanent magnet at room T , and then dissolving with water from a manually actuated syringe. Finally, ¹³C NMR measurement at 300 K and 1 T is made within a few seconds of dissolution. We obtained up to 1500-fold enhancement, for example, from polarization at 2.1 K for 24-72 h, and up to 400-fold enhancement from 4 hrs of polarization at 6 K. Several thousand-fold gains are possible with reduced T and increased polarization time. Waiting times may be scaled away by polarization of multiple samples, not to mention the potential for coupling large-scale preparation with sample transport.

We will detail these experimental results and corresponding apparatus, define underlying physical phenomena that govern the polarization source (i.e., ¹³C Boltzmann vs. ¹H-to-¹³C thermal mixing), and explain a protocol to usefully manipulate the T_1 vs. T valley by annealing a neat, unadulterated sample.

Sustainable Ultra-Low Temperatures for Magic Angle Spinning combined with Dynamic Nuclear Polarization

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Magic Angle Spinning combined with Dynamic Nuclear Polarization (MAS-DNP) has recently been shown to be not only applicable but highly valuable for studying a wide range of materials. Its successful implementation was due to a desire to continually push the boundaries of sensitivity for NMR experiments. However, there is still room to push much further. Currently, equipment limitations exist due to technological and cost issues and most MAS-DNP experiments are performed at approximately 100 K. There is a large interest in lowering the operational temperature even further but this requires new technological advances to make it viable. In this presentation the substantial gains expected by descending the temperature below 100 K will be detailed. Furthermore, the hardware we have designed and built to achieve sustainable MAS in the temperature range of 30 – 300 K will be shown and described. Finally, results using this equipment in the ultra-low temperature range (30 - 100 K) will be exhibited.

CPI Extended Interaction Klystron technology for DNP

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Dynamic Nuclear Polarization (DNP) and Electron Spin Resonance (ESR) are driving the need for high power, compact sub-mm wave sources. Communication & Power Industries has responded by developing pulsed and continuous wave (CW) amplifiers (EIK) and oscillators (EIO) with tens of Watts of power at frequencies from 95 GHz to 264 GHz. Extended Interaction Klystron technology preserves the ruggedness and high power capability of the conventional klystron while achieving enhanced power, bandwidth and efficiency at millimeter and sub-millimeter wavelengths, while using moderate electron beam voltages.

Extended Interaction Amplifiers and Oscillators are compact devices that are simple to use and maintain. They provide an RF signal with the high frequency and amplitude stability required for DNP and have enough bandwidth or tuning range to cover the electron spin resonance (ESR) spectrum of hundreds of MHz. In addition, the EIKs are magnetically shielded and may reside close to the NMR magnet, thereby minimizing the significant waveguide losses and simplifying installations. We report here on hardware developments, which meet these goals and offer new opportunities for DNP research.

The design and test results will be presented for a 5 W CW 187 GHz amplifier, a 5 W CW 264 GHz oscillator, and a 20 W pulsed 264 GHz amplifier. All three are compact (< 8 kg) devices based upon Extended Interaction Klystron technology, and operate from commercially available power supplies

Microwave Frequency Modulation to Enhance Dissolution Dynamic Nuclear Polarization

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During the last decade, Dissolution Dynamic Nuclear Polarization (D-DNP) has emerged as one of the most revolutionary and powerful techniques in NMR to enhance nuclear spin signals by up to five orders of magnitude [1]. Nowadays, a broad range of applications from metabolic processes to *in vivo* imaging has emerged thanks to this improvement in sensitivity [2].

D-DNP is usually performed with a glassy matrix containing free radicals (TEMPO, Trityl, etc.) and the metabolites of interest ([1-¹³C]pyruvate, [1,2-¹³C]acetate, etc.) by irradiation with monochromatic microwaves in the vicinity of the electron spin resonance (ESR) frequency at 1.2 K and 3.35, 5 or 6.7 T. Different DNP mechanisms like Thermal Mixing (TM), Cross-Effect (CE) and Solid Effect (SE) are usually involved in the enhancement or depletion of the polarization depending on the offset between the microwave frequency and the center of the ESR line.

It has been shown recently by Hovav *et al.* [3] that DNP by CE and SE can be improved by using frequency-modulated microwave irradiation at $B_0 = 3.34$ T in the temperature range $10 < T < 50$ K. We demonstrate that this approach can also be applied to D-DNP at higher magnetic fields ($B_0 = 6.7$ T) and lower temperatures ($1.2 < T < 4.2$ K.) The effect of frequency modulation (*fm*) has several virtues: (1) a gain in polarization by a factor $\varepsilon_{fm} > 3$, (2) an acceleration of DNP build-up rates by a factor $\kappa_{fm} > 10$, (3) a reduction in radical concentration by at least a factor 2, (4) a concomitant extension of $T_{1\rho}(^1\text{H})$ which improves the efficiency of cross-polarization from protons to other nuclei of interest such as ¹³C, ¹⁵N or ⁶Li, and (5) a reduction of the required microwave power [4].

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Novel ^{129}Xe SEOP polarizer for medical and material studies

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The introduction of hyperpolarized noble gases ^3He and ^{129}Xe delivered a great tool for growing number of applications, ranging from medical imaging [1, 2, 3] to spectroscopy studies. Rising requirements for large volumes of hyperpolarized gases could be realized by efficient polarizers and such as a novel polarizer for ^{129}Xe presented here. This high-scale production polarizer works based on the Spin Exchange Optical Pumping (SEOP) method. The specific properties of xenon, mostly arising from the large polarisability of its electron cloud, makes this noble gas a very interesting NMR probe for biological systems [4] and is commonly used in non-invasive lung diagnosis for MRI applications. Three main parts of this polarizer will be presented: the high-power laser system for rubidium optical pumping, the high-volume SEOP cell and the cryogenic accumulation system for hyperpolarized ^{129}Xe . This overview of the motivation and current status of our SEOP polarizer project and research on processes like spin-exchange and relaxation mechanisms are the main topics of this presentation.

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Microfluidic gas-flow imaging by parahydrogen-induced polarization and remote-detection NMR

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Microfluidic devices provide control over a process with capabilities that exceed those for conventional macroscopic systems. NMR imaging is one of the rare candidates for in situ monitoring of physico-chemical processes, since it has versatile and rich toolkit for mass transport visualization. However, conventional NMR imaging techniques suffer from low sensitivity, which makes studies of microfluidic reactors practically impossible. We show that substantial sensitivity boost can be achieved by combining remote-detection (RD) NMR and parahydrogen-induced polarization (PHIP) as has been demonstrated recently for microfluidic gas-flow [1]. Moreover, we used this technique for imaging the mass transport and progress of gas-phase hydrogenation reaction inside cylindrical micro-scale packed-bed reactors of 150-800 μm in diameter [2]. At the same time, we introduce the concept of microfluidic PHIP polarizer as a methodology for continuous production of hyperpolarized substances. We show that the combined PHIP-RD technique can provide information about reaction product distribution, mass transport and adsorption effects in the model micro-scale reactors during their in situ operation.

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Talks in Working Group 2 and 3

Theoretical Understanding of Hyperpolarization Strategies

**Strategies to Minimise the Effect of Relaxation on
Spin Hyperpolarization**

Organized by

Konstantin Ivanov, Alberto Rosso

Hans-Martin Vieth

Room-Temperature ^{13}C Hyperpolarization in NV-doped Diamonds: A Combined Laser and Microwave Irradiation Technique at Arbitrary Fields

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Recent years have witnessed an increased demand for generating and detecting highly polarized nuclear spins in physical, chemical, biological and medical applications. Hyperpolarization invokes a huge boost in sensitivity and speed of Nuclear Magnetic Resonance (NMR) and Magnetic Resonance Imaging (MRI), and can be of great benefit in preparing and controlling quantum information [1]. Bulk hyperpolarization of ubiquitous ^{13}C species can be achieved by cryogenic Dynamic Nuclear Polarization (DNP), however, from a microscopic point of view, the underlying mechanisms are not very well understood. Nitrogen-vacancy (NV) doped diamonds have a number of intriguing properties, making them excellent candidates to act as room-temperature hyperpolarization sources for nuclear spins [2,3], as well as model systems for further investigations of the bulk-hyperpolarization mechanisms [4]. So far, however, universal applications of these highly polarized nuclear spin states are prevented by the need of established methods for stable and robust electron \leftrightarrow nuclei polarization transfers, demanding extreme fine tunings of magnetic fields and ultrasensitive alignments of single-crystal diamonds. Here we present an alternative approach for achieving these polarization transfers, compatible with a broader range of magnetic field strengths [4]. By combining microwave and laser irradiation of electron/nuclear spin systems an imbalance in the spin populations can be imposed on nuclei in the close vicinity of the NV defect with a selectivity that can range down to a single polarized nucleus. Successive ^{13}C NMR experiments based on shuttling samples between optical and NMR setups, demonstrate that the ensuing hyperpolarization is then extended throughout the nuclear bulk ensemble. This new physical process could allow a refinement of existing DNP theories and open new perspectives on ensemble and nanoscale applications [5] for NMR/MRI and quantum information processing.

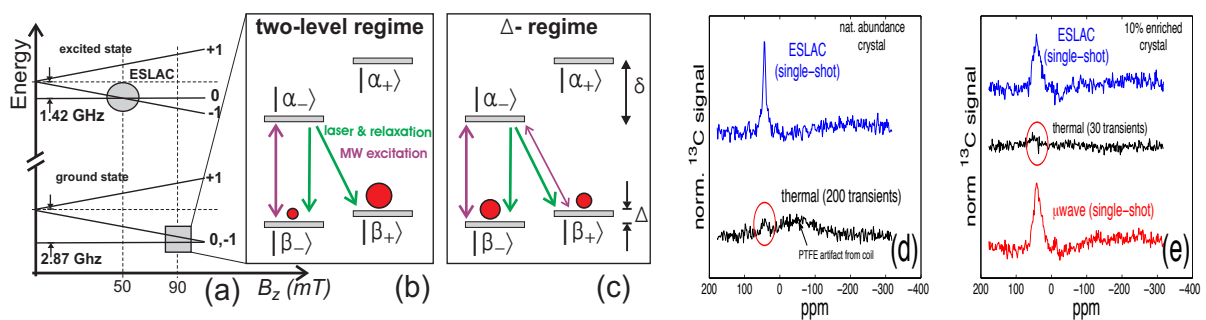


Figure 1: Simplified schematic energy diagram (a) of a strongly-coupled NV- ^{13}C two-spin system as a function of an axial magnetic field B_z with (b,c) hyperfine-induced splittings (δ , Δ) and mixings of energy levels ($|\alpha_{\pm}\rangle$, $|\beta_{\pm}\rangle$). Under optical pumping and on-resonant MW irradiation ($|\beta_{-}\rangle \leftrightarrow |\alpha_{-}\rangle$) polarization transfer processes can be established. (d,e) After a rapid sample shuttling into a high-field magnet, the ensuing bulk ^{13}C NMR signal (colored lines) can be compared to thermally-equilibrated, high-field NMR signal (black line). An enhancement by two orders of magnitude is observed, corresponding to a nuclear polarization of up to 0.4% (nat. abundance) and 0.1% (enriched crystal).

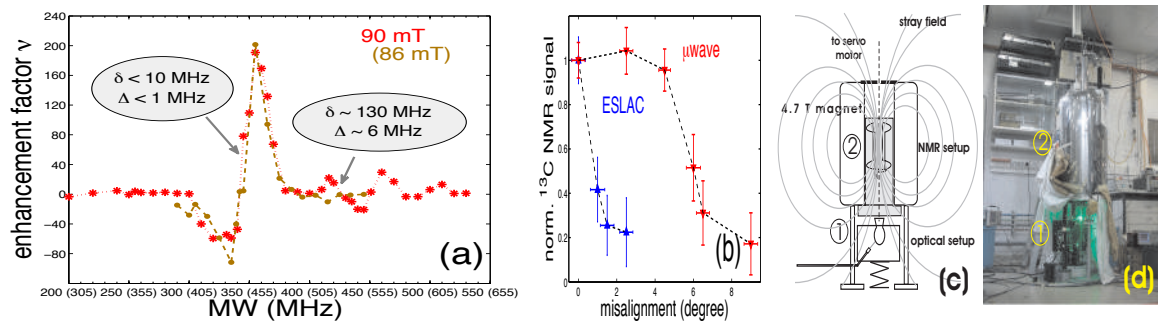


Figure 2: (a) High-Field ^{13}C NMR enhancement factor v observed as a function of the μ wave frequency for $B_0 = 90$ mT and 85 mT. For the strongest hyperfine splittings ($\delta \sim 130$ MHz, $\Delta \sim 6$ MHz) the observed bulk NMR signal originates from an ensemble of polarized nuclei in one of the four nearest-neighbor positions. The proposed method shows comparable enhancement factors at arbitrary fields and an increased robustness (b) against imperfections in the sample alignment. Schematic illustration (c) and image (d) of the optical/NMR setup and the sample shuttling apparatus.

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Paramagnet-Induced Signal Quenching and Relaxation in MAS DNP

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Dynamic nuclear polarization (DNP) is a powerful technique to boost the sensitivity of magic-angle spinning (MAS) NMR as has been demonstrated on various accounts in biomolecular and materials science applications.^[1] During MAS DNP the large electron spin polarization is transferred to the nuclear spins, most commonly ^1H , via two possible mechanisms: the solid effect (SE) or the cross effect (CE). Once the enhanced ^1H polarization is available, it can be transferred to other nuclei (e.g., ^{13}C , ^{15}N) in typical multi-resonance NMR experiments. Alternatively, these nuclei can be directly polarized.

The electron spin polarization is provided by paramagnetic polarizing agents, which in most cases have to be added to the sample. These paramagnets not only act as polarizing agents, but also may induce enhanced nuclear relaxation or signal quenching due to strong electron–nuclear interactions. The mechanism of these effects have been well known for several decades as derived in seminal works by Bloembergen, Solomon, and Blumberg,^[2] and is based on temporal changes of the local field at the nucleus, induced by spatial (*i.e.*, dynamics) as well as spin (*i.e.*, electronic relaxation) fluctuations. However, under the cryogenic conditions where MAS DNP is usually performed these theories cannot be easily applied, and the highly complex interplay between spatial and spin fluctuations renders an analytical treatment unfeasible. Additionally, modulation of the electron-nuclear energy levels by MAS has been introduced recently as a fundamental concept to understand CE DNP and might play an equally important role in paramagnet induced quenching and relaxation.^[3]

In this presentation the influence of the polarizing agent on the nuclear relaxation and signal quenching will be demonstrated on the example of four different polarizing agents, each representing a class of polarizing agents typically used in solid-state DNP. The differences and similarities between these systems will be discussed and correlated with (1) the main active DNP mechanism for each polarizing agent, (2) the EPR properties of each polarizing agent, (3) the DNP efficiency. Despite the potentially detrimental effects due to signal quenching, the sensitivity increase by MAS DNP is generally outstanding; however, a compromise between enhancement of nuclear polarization and coherence loss is often necessary for optimal sensitivity.^[4] Finally, an outlook will be given on ongoing efforts to further investigate the mechanism of NMR signal quenching and to explore novel approaches to DNP.

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Temperature evolution of the electron-nucleus contact in pyruvic acid DNP

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Pyruvic acid (PA) can be considered as a prototype system to study Dynamic Nuclear Polarization (DNP) via Thermal Mixing (TM). Recently several studies performed around 1 K have shown that the TM regime is highly efficient in PA labeled with ^{13}C when it is doped with a concentration of trityl radicals of the order of 10 mM^{1,2}. Nevertheless, in very few works the effect of raising the temperature (T) on the nuclear relaxation and polarization parameters and the role of the properties of the matrix formed by the polarized molecules and radicals has been addressed.

We present an NMR study of PA and PA containing trityl radicals performed as a function of T between 1.6 and 5 K at 3.46 T, in order to clarify the properties of the lattice dynamics of the PA and its effect on DNP. The investigations were performed utilizing both ^{13}C nuclei and ^1H nuclei, since the latter are not involved in the TM. Notably the study of ^1H dynamics in this T range has not been previously reported in the literature and can eventually help to identify the relaxation processes involving the coupling with the lattice dynamics.

In particular we show that the nuclear relaxation rates can be explained by considering the presence of a glassy dynamics in PA. Nevertheless, although the nuclear relaxation rates are considerably affected by the glass treatment and change upon thermal history, the polarization times and polarization levels of ^{13}C at the lowest T are scarcely dependent on these parameters. Since the electronic relaxation times T_{1e} are mainly dependent on the radical concentration, accordingly, this observation allows to attribute to the electronic relaxation channel the leading role in determining the low temperature DNP properties of these systems. Definitely, it is shown that, in good agreement with the predictions of recent theoretical models^{3,4,5}, under 2-3 K the TM process in PA is well described by considering a good thermal contact between the ^{13}C nuclear spin and electron spin reservoirs, i.e. $T_{1e} \gg T_{\text{ISS}}$, the electron-nucleus contact time. On the contrary, on raising T the TM occurs through a less efficient contact, probably due to the shortening of T_{1e} which becomes of the order of T_{ISS} .

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Sensitivity enhancement in solution by DNP and para-H₂

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Applications of para-H₂ supported hyperpolarization will be given with respect to enhancement factors in dependence of the molecule under investigation (1) as well as the technical implementation used involving different set-ups of the polarizer.

If time permits an update on the shuttle DNP will be given that allows for repetitive hyperpolarization of samples of small biomolecules (2). 2D as well as 1D experiments will be shown and also further developments will be discussed that follow from the development of this device.

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New Insights into the Role of the Electrons during DNP on Solids

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Three main mechanisms have been used to explain DNP: the Solid Effect (SE), the Cross Effect (CE), and Thermal Mixing (TM). The SE and CE mechanisms rely on microscopic processes, whereas the TM mechanism describes macroscopic systems and is based on the spin temperature formalism. In the latter it is assumed that the state of the spin system is given by a set of spin temperature coefficients, as was demonstrated experimentally by Atsarkin (1971) and Atsarkin and Rodak (1972). The TM mechanism is commonly used to explain the similarity of DNP frequency-sweep spectra measured on different nuclei in the same sample.

To test the relevance of the spin temperature hypothesis for typical DNP samples we performed electron double resonance (ELDOR) measurements on samples containing 40 mM TEMPOL (at 20-3 K) and 15 mM OX63 Trityl (at 30-3 K) radicals in a glass forming solvent. We observed that the frequency dependent electron polarization profiles do not agree with the predictions of spin temperature theory.

In our previous work we considered the microwave driven SE and CE as the mechanisms responsible for the measured DNP spectra, taking into account the electron and nuclear relaxation times but neglected the effect of the electron spectral diffusion (SD) process. Here we present the implications of SD for the SE and CE mechanisms, and we show based on our recent ELDOR measurements described above as well as those by Granwehr and Kockenberger (2008), that this cannot be neglected. In particular we will describe the “indirect CE” mechanism, which is a result of the SD induced frequency profile of the electron polarization within the EPR lineshape and the CE state mixing, in analogy with the CE mechanism described by Hwang and Hill (1967) and Wollan (1976). This mechanism can explain the similarity between the DNP lineshapes and the maximum enhancements of different nuclei in the same sample, without relying on spin temperature arguments. This will be demonstrated by DNP measurements on partially deuterated glass forming samples containing TEMPOL.

Recent Advances in Continuous Hyperpolarization using SABRE

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By subjecting an appropriate SABRE [1,2] sample to a magnetic field of $B_S \approx 5$ mT, parahydrogen (pH_2) spin order is continuously transferred to a substrate. Whereas at low field the chemical shift resolution is lost, the advantages polarization and detection at low field B_S are quite interesting: there is no conventional T1 decay and the polarization re-covers swiftly after its full or partial depletion by excitation pulses. Furthermore, the source of spin order, pH_2 , is not affected by excitation pulses neither, and fresh polarization is delivered even during repetitive-pulsing experiments. Altogether, these properties are very interesting for the biomedical application of hyperpolarization.

As a proof of concept, fast magnetic resonance imaging (MRI) was demonstrated using a commercial scanner, set to cycle between B_S for hyperpolarization and the Earth field B_E for detection[3] (Fig. 1, Terranova, Magritek, NZ).

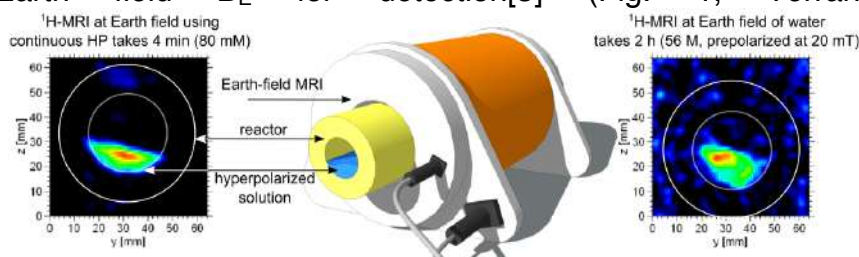


Figure 1: Two-dimensional projection images of continuously hyperpolarized, low-concentration agents with an in-plane resolution of 1mm² were acquired in 4.16 min (left: 3 ml, 80 mM), whereas 2.16 h were required to image water at much higher ¹H concentration at 20 mT (right: 6 ml, 56 M, 32 averages, prepolarized at 20 mT).^[3]

In addition, we conducted fast, low-field NMR of a continuously re-hyperpolarizing substrate at ≈ 5 mT using a recently described setup.[4] Reference to a thermally polarized sample allowed to estimate the absolute polarization yield.[5] By variation of the recovery delay in between 90° excitations, a mono-exponential recovery of hyperpolarized signal was observed with a time constant of 5 s (Fig. 2).[3]

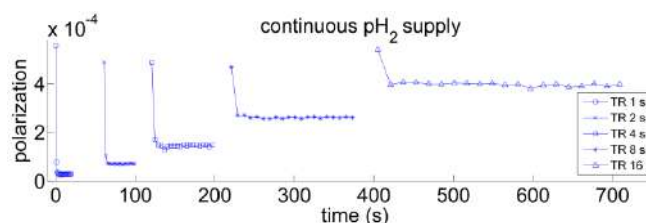


Figure 2: Absolute polarization produced during the continuous hyperpolarization process. Each data point represents the peak area of a hyperpolarized pyridine resonance as monitored by a cascade of 90° excitation pulses that are separated by a variable recovery delay (TR/s). After depletion by excitation, the hyperpolarization level recovers with a time constant of 5 s to a level of 10^{-3} which equates with a thermal ¹H-polarization field of between 10^2 and 10^3 Tesla.^[3]

To gain insight into the underlying physics of this effect, we relied on the established density operator formalism e.g. as described by Levitt[6] which was used to simulate (high-field detected-) SABRE before.[7]

A distinct distribution of observable substrate polarization was found, depending on the magnetic field B_S and the duration of pH_2 -substrate interaction t_c (Fig. 3).[8]

In conclusion, continuous hyperpolarization with pH_2 offers interesting perspectives for magnetic resonance beyond relaxation, including fast low-field imaging. Simulations of this effect exhibited a strong dependency on field strength and interaction time, which may be exploited for future catalyst design. The key hurdle toward biomedical application is the adaptation of this method to biological conditions.

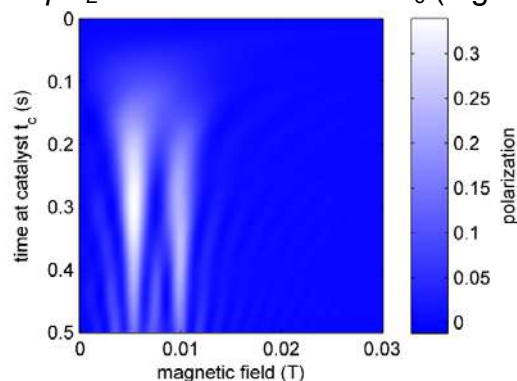


Figure 3: Theoretical assessment of continuous hyperpolarization: transfer of observable polarization from pH_2 to a 2-spin- $\frac{1}{2}$ substrate as function of magnetic field B_S and interaction time t_c .

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The role of hyperfine coupling in solid-state electron-nuclear polarization transfer

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Hyperfine coupling mediates polarization transfer between electron and nuclear spins and is thus central for theoretical description of almost all methods for nuclear hyperpolarization. In many cases the transfer can be understood in terms of a change in the Hamiltonian that leads to level mixing. Transfer is then optimal at a matching condition that corresponds to an avoided level crossing. Depending on the type of spin system (one or more electron spins directly or indirectly coupled to the nucleus at the time scale of the transfer) and on other spin Hamiltonian terms, different types of such avoided level crossing can occur. In the solid state level mixing and transfer depend on a pseudo-secular component of hyperfine coupling that allows for factorization of Hilbert space in multi-nuclear spin systems in the absence, but not in the presence of microwave irradiation. The lecture will show why and will discuss phenomena such as matched irradiation and hyperfine decoupling.

Adiabatic elimination and stochastic unravelling in multi-spin quantum-mechanical simulations of DNP in solids

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The physically reliable quantum-mechanical description of the dynamic nuclear polarization (DNP) in solids would generally require a density operator formalism involving numbers of spins comparable with the Avogadro number. For common polarizing agents and wide physical conditions, two DNP mechanisms can be considered as dominating: the solid effect and the cross effect mechanisms. In this case, statistical models involving one or two electronic spins surrounded with nuclear spins are rather suitable to describe the spin dynamics. Depending on concentrations, the number of surrounding nuclei can be between tens and tens of thousands. This makes calculations in the full Liouville space still infeasible and thus needing effective space reductions.

We have recently shown that, under physically reasonable conditions, this difficulty can be overcome using the following two-step technique. First, we demonstrated that the nuclear polarization build-up curves are well described by a reduced master equation obtained by adiabatic elimination of non-Zeeman spin orders from the full Liouville space. Second, we found that the reduced master equation can be written in the purely incoherent Lindblad form enabling us to apply a method of stochastic unravelling in Hilbert space, a computational analogue of the dynamic Monte Carlo method. This makes possible numerical simulations within the solid effect and the cross effect DNP mechanisms involving up to hundreds of nuclear spins within reasonable computation times. An additional advantage of the approach is that it enables parallel calculations, so fast multi-processor supercomputers can now be used to significantly accelerate simulations.

In this talk, mathematical and computational aspects of the above approach will be briefly presented along with numerical results supporting the theory. Some open questions, such as reliable descriptions of relaxation processes as well as spin diffusion, spectral diffusion and thermal mixing effects, will be suggested for a discussion.

Manipulating spin hyper-polarization by means of adiabatic switching of a spin-locking RF-field

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A new method has been proposed allowing one to convert initial multiplet spin order into polarization of almost any desired kind. It is based on hyper-polarizing a system of scalar coupled spins in the presence of a strong RF-field, which is subsequently slowly (adiabatically) reduced to zero. The technique can be useful for manipulating hyper-polarization, in particular, in cases where multiplet spin order gives the main contribution to hyper-polarization. The method allows one not only reversing the sign of the multiplet polarization but also converting it into net hyper-polarization without any loss of the spin order. In contrast to multiplet spin order the contributions coming from net polarization do not disappear in the NMR spectrum in the presence of line broadening. Therefore net hyper-polarized signals can be used in NMR spectroscopy and imaging in combination with standard pulse sequences. For instance, our technique can be applied to the case of PHIP, which gives very strong hyper-polarization resulting in NMR enhancements of up to 10,000; in contrast, the original polarization is purely of the multiplet kind. For the two-spin system we were able to show theoretically and experimentally that PHIP can be fully converted into net spin order: for instance, by properly setting the RF-field frequency one can convert the initial state population pattern into one where only the $\alpha\alpha$ and $\beta\beta$ spin states are populated; therefore both spins will get net polarized. The method can also be extended to higher-spin systems, which initially carry only multiplet polarization, thus allowing one to create net hyper-polarization.

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PHIP Hyperpolarization of Fluorine: Applications, Examples and Problems

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Fluorinated molecules are of huge interest as chemical sensors in liquids. In combination with ^{19}F NMR spectroscopy they allow the detection of changes in temperature or pH-value and an interactions with other molecules. Especially for the examination of biological samples or *in vivo* measurements, such as metabolic studies or MRI, low concentrations are often a hindrance. One technique to overcome the disadvantage of low spin density *in vivo* is the Parahydrogen Induced Polarization (PHIP)[1,2,3]. Here, the hydrogenation of different fluorinated aromatic and linear substrates using parahydrogen is presented. T_1 measurements and different solvents are investigated with respect to the achieved signal enhancements.

As model compounds precursors such as 3-fluorophenylacetylene, (2E)-2-acetamido-3-(2,5-difluorophenyl)acrylic acid, perfluoroalkenes and -alkenes were chosen for hydrogenation with about 50 % enriched parahydrogen (6 bar) in different vented solvents. Immediately after hydrogenation in earth field and transport into detection field, ^{19}F NMR spectra were acquired using a Bruker WB300 spectrometer.

In case of hydrogenation of (2E)-2-acetamido-3-(2,5-difluorophenyl)acrylic acid the product signals shifted clearly. It can be observed that the fluorine in ortho position (negative phase) has a higher chemical shift sensitivity but a smaller enhancement, while fluorine in meta position (in-phase signal) shows a slightly larger SE and smaller chemical shift dependency.

^{19}F -NMR spectrum of hyperpolarized (perfluoro-n-hexyl)ethene shows increased signals of fluorine bonded at C-3', C-4', C-7' and C-8'. An unexpected enhancement of the signal at about -82 ppm (CF_3 -group, C-8') can be utilized for ^{19}F MRI.

So far, the potential of ^{19}F hyperpolarization is widely unexploited. The polarization transfer from the new bonded hydrogen atoms to fluorines is not clarified in detail. Our experiments show a T_1 -related dependence of the signal enhancement in different solvents which of course is evident. Here, it becomes clear that particularly attractive hydrophilic solvent mixtures causes a decrease of the T_1 time respectively of the achievable SE, which emphasize the need for adapting long living techniques to fluorine. A strong polarization transfer over a long distance could be observed in linear perfluoroalkenes and -alkanes measured in organic solvents.

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Metal ions and DNP - considerations over the impact of electronic properties on DNP

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Some paramagnetic metal ions have been shown to be of interest for DNP studies. For instance isotropic or nearly isotropic gadolinium and manganese are suitable polarizing agents in rotating solids at the liquid nitrogen temperature (1). This holds true as long as the $1/2 \leftrightarrow 1/2$ transition is sharp enough so as to give efficient solid effect. Gadolinium is also used to improve the efficiency of DNP in static samples at lower temperatures, where the $7/2$ state may dominate and make it not amenable to be a polarizing agent (2). Theoretical arguments also support the hypothesis that some slow relaxing metal ions could be used as polarizing agents in solution (3).

We here discuss the role of the electronic structure of the metals in selected cases:

A) we discuss the effect of gadolinium ions on trityl relaxation and its outcome in low temperature DNP

B) a highly symmetric chromium complex is used for MASDNP and its temperature-dependent zfs is investigated

C) the coupling factor of overhauser dnp is derived from field dependent relaxometry measurements for several ions.

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DNP on Heteronuclei: Theory and Experiments

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DNP enhancement frequency spectra of ^{13}C enriched molecules in samples containing the trityl radical show significant positive and negative enhancement lines outside the EPR spectrum at frequencies $\omega_e \pm \omega_{1\text{H}} \pm \frac{1}{2} \omega_{^{13}\text{C}}$. These features cannot be explained by the “Double Solid Effect” (double SE), previously observed in a sample containing BDPA with ^2H nuclei [1,2], since in the double SE the peaks should appear at $\omega_e \pm \omega_{1\text{H}} \pm \omega_{^{13}\text{C}}$. To explain these experimental observations Liouville space simulations were conducted for the following three- and four-spin systems: $\{^1\text{H}-e-^{13}\text{C}\}$ and $\{^1\text{H}-e_a-e_b-^{13}\text{C}\}$.

The double SE mechanism is present in the three-spin system; however, our observations require the four-spin system. In this study we discuss DNP on this system also taking into account effects caused by nuclear spin diffusion and electron spectral diffusion processes. It was previously shown by Cox et al. [3] that there exists a transfer mechanism between the polarizations of heteronuclei. To study this transfer mechanism we performed DNP experiments on partially deuterated samples containing TEMPOL and followed the fast cross-talk between the ^2H - and the ^1H -polarizations in these samples.

To describe these transfer processes we again consider the four-spin system $\{^1\text{H}-e_a-e_b-^{13}\text{C}\}$ and demonstrate that high order CE conditions are responsible for our experimental observations.

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Sabre hyperpolarization at low concentrations

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SABRE is a nuclear spin hyperpolarization technique based on the reversible association of a substrate molecule and parahydrogen ($p\text{-H}_2$) to a metal complex. During the lifetime of such a complex the spin order of $p\text{-H}_2$ is transferred to the nuclear spins of the substrate resulting in strongly enhanced NMR signals. This technique is generally applied at relatively high concentrations (mM), in large excess of substrate with respect to metal complex. Dilution of substrate ligands below stoichiometry determines a progressive decrease of signal enhancement, which precludes the direct application of SABRE at low concentrations (μM). We have recently shown [1] that by addition of a suitable ligand to the solution, the efficiency of SABRE at low substrate concentration can be restored, allowing NMR detection below $1\mu\text{M}$ in a single scan. Preliminary results on the application of SABRE to complex mixtures at low concentrations will be illustrated.

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Talks in Working Group 4

**Strategies to Maximise the Information that can be Acquired Using
Hyperpolarized Spin Systems**

Organized by

Lucio Frydman, Jim Wild

Accelerating Hyperpolarized MRI by Exploiting Spatiotemporal Correlations and Sparsity

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Data undersampling is a key strategy in hyperpolarized MRI to achieve appropriate spatiotemporal resolution within the limited time window available. Different strategies have been proposed to reconstruct incomplete datasets. These methods can be classified as linear and non-linear reconstruction methods. For both approaches, suitable transform operations are essential to either compress or sparsify the data. Of particular value are transform operations along the time axis of time-resolved, dynamic data series. To this end, methods utilizing temporal basis functions of various kinds have proven to be valuable. In the context of metabolic imaging, integration of kinetic models into image reconstruction may be used to further restrict the range of solutions to physiologically meaningful subsets.

In this presentation, an overview about linear and non-linear reconstruction methods from undersampled data will be given and their application to hyperpolarized lung and cardiac imaging discussed. Advantages and limitations of each approach will be highlighted based on a unified mathematical framework.

Fast Padé Transform accelerated CSI for hyperpolarized MRS

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Purpose: The aim of this study was to demonstrate that the Padé approximant in form of Fast Padé Transform (FPT), can reduce the scan time of hyperpolarized CSI, without sacrificing the robustness and flexibility and secondly to demonstrate a fully automated and direct quantification of the FPT.

Methods: Hyperpolarized [1-¹³C]pyruvate CSI data was processed with the FPT and compared with a spectral analysis using the Fast Fourier transform (FFT). The unique property of Frossiart filtering in the FPT showed unique results for noise cancellation of spurious signals.

Conclusion: Here we show the use of the FPT can reduce the sampled spectral dimension 2-6 times, without sacrificing the spectral resolution required, thereby gaining temporal resolution and that oppose to the FFT counterpart the FPT directly yields exact quantification of the spectral components at no extra expense.

Tests of RF phase encoding in low-field MRI

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Gradients of B_1 phase can replace the gradients of B_0 magnitude used in conventional MRI for spatial encoding of the magnetisation. So far this method, called TRASE (Transmit Array Spatial Encoding), has been demonstrated at $B_0 = 0.2\text{T}$ and prospects have been discussed for MRI at higher field strength, where the elimination of fast and noisy B_0 gradient switching would be beneficial [1].

For low-field MRI, where hyperpolarisation methods can be employed to obtain high-SNR images, the adverse effects of concomitant gradients put a limit to the resolution achievable with B_0 gradients. To assess the potential of TRASE imaging in the millitesla range, we have implemented an additional spiral RF coil [2] in a 15-cm bore resistive magnet, equipped with a usual (uniform-field) RF coil and imaging gradient coils for operation up to 2.5 mT [3]. RF phase encoding in the axial direction is obtained using series of alternating 180° flips by the two RF coils. The efficiency of this scheme is compared to that of encoding with B_0 -gradient pulses both in 1D and 2D imaging of water samples.

The limitations associated with the use of short and intense RF pulses will be discussed (due, e.g., to the counter-rotating parts of the linear RF fields and to the concomitant B_1 field component for the spiral coil), as well as the extension of the method to hyperpolarised samples with non-renewable magnetisation (optically pumped He3 gas in our experiment).

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Spectroscopy of dissolved ^{129}Xe in human brain at 1.5T

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Introduction: Hyperpolarized (HP) ^{129}Xe , when inhaled into the lungs, dissolves in the blood via the alveolar-capillary pathway and can be used to study perfusion in other organs. HP ^{129}Xe has a large range of chemical shift and can be used to study uptake in the human brain when dissolved ^{129}Xe is transferred across the blood-brain barrier to white matter, grey matter and cerebral lipids. The dynamics of ^{129}Xe uptake in the human brain has been previously measured at 3.0T¹; this study reported detection of NMR peaks from ^{129}Xe dissolved in white and grey matter, with no evidence of peaks from blood or cerebral lipids, despite what has been observed previously in the rat brain³. An earlier study at 1.5T in the human brain exhibited only a single dominant peak from brain tissue². The motivation of our work is to demonstrate dynamic spectroscopy of ^{129}Xe in the human brain at 1.5T using optimized RF brain coil designs at 17.6 MHz. In addition we have developed an uptake model with spin density and flip angle (FA) variation to account for the ratio of grey matter to white matter by volume.

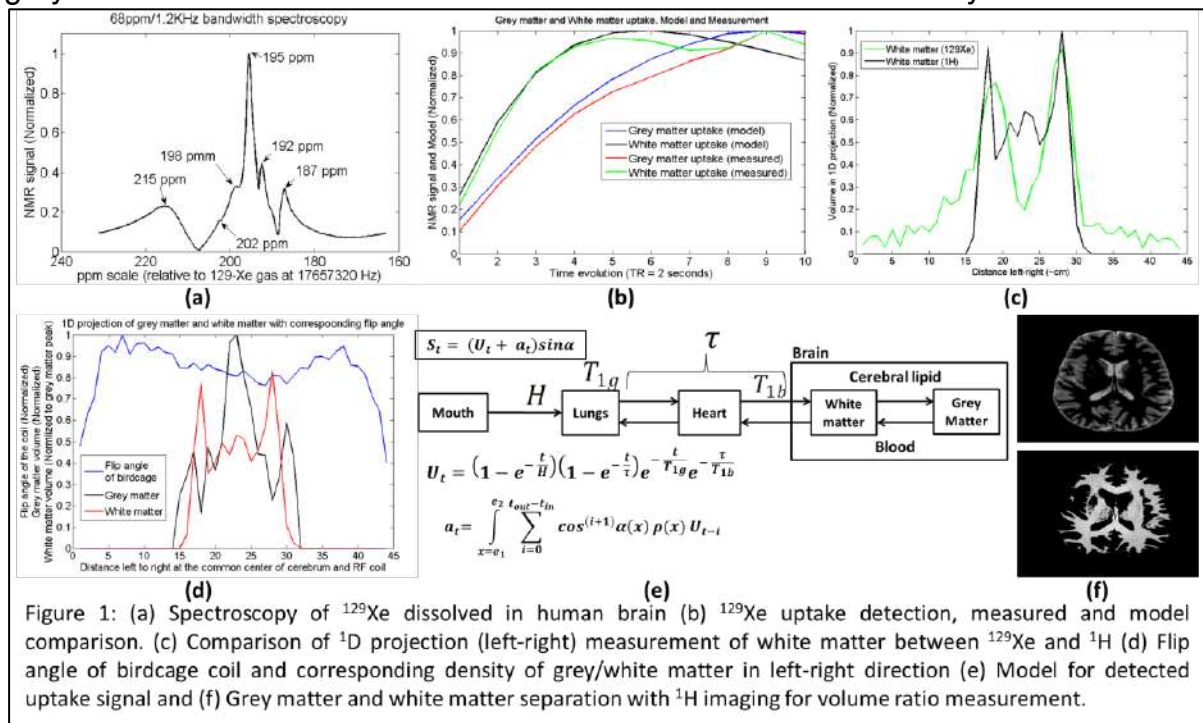


Figure 1: (a) Spectroscopy of ^{129}Xe dissolved in human brain (b) ^{129}Xe uptake detection, measured and model comparison. (c) Comparison of ^1D projection (left-right) measurement of white matter between ^{129}Xe and ^1H (d) Flip angle of birdcage coil and corresponding density of grey/white matter in left-right direction (e) Model for detected uptake signal and (f) Grey matter and white matter separation with ^1H imaging for volume ratio measurement.

Method: Three different RF coils were constructed, one birdcage coil with eight legs and two quadrature transmit-receive coils (conventional loop and spiral design). In-vivo spectroscopy of the human brain with HP ^{129}Xe was performed on a GE 1.5T (Signa HDx) system. HP ^{129}Xe gas (86% ^{129}Xe , 30~60% polarization) was inhaled in doses of between 300mL to 1L. All subject tolerated the breath-hold well and vital signs were monitored throughout the scan. Whole-brain ^{129}Xe spectra were acquired using a pulse-acquire sequence, with an inter-pulse delay (TR) of 2s. FA was 90° , with an RF pulse-width of $500\mu\text{s}$ (50mW average power) and bandwidth of 1.2 kHz, Centre frequency was set to 197ppm downfield from the ^{129}Xe gas peak. An uptake model as shown in Fig 1(e) was developed considering the flip angle variation and corresponding spin density dissolved in the putative grey matter and white matter

compartments as shown in 1(d). The model was fitted to data acquired with various flip angles as shown in 1(b). The ratio of grey matter to white matter by volume was measured and compared with results from ^1H imaging as shown in Figure 1(c) and (f).

Result: The ^{129}Xe brain spectrum shows peaks attributable to ^{129}Xe in cerebral lipids(187 ppm), white matter(192 ppm), grey matter (195 ppm) and blood(198, 215 ppm) as shown in Fig 1(a). The ratio of grey matter to white matter for a particular volunteer (M,31y) was measured to be 1.7 from ^{129}Xe spectroscopy and 1.59 from ^1H imaging (the latter with an 8% error). The ^{129}Xe uptake at flip-angle 20° , 45° and 90° correlated well with the model considering the following: inhalation time (H) = 4s, T1 relaxation of ^{129}Xe in gas = 25s, T1 relaxation of ^{129}Xe in blood = 10s, Transit time constant of ^{129}Xe from lung to brain = 4s, time take from the blood to enter-exit grey matter = 10s/white matter = 5s and finally the flip angle and density of grey/white matter as was measured. The grey/white matter volume fraction measurements from ^{129}Xe spectroscopy in a 1D projection in the left-right direction correlated well with a similar projection in ^1H imaging.

Discussion: The difference in the ratio of grey matter to white matter volume between ^{129}Xe spectroscopy and ^1H measurement may be explained by the fact that the dissolution co-efficient of ^{129}Xe in grey matter and white matter has ratio of 1.2^{4,5} and ^1H measurement considered only cerebrum region with 8~12% error (grey-white overlap region). The ratio of grey matter to white matter measured from ^{129}Xe spectroscopy varies with flip angle, for 20° flip angle the ratio is 1.3 and for 90° flip angle the ratio is 1.7. This may be due to the fact that, the enter-exit time of blood in white matter is faster than grey matter. Hence, an accurate uptake model considering flip angle variation with spin density determines the measurement error in the grey matter to white matter volume ratio.

Conclusion: In this work we have demonstrated multiple dissolved ^{129}Xe peaks in the human brain in-vivo at 1.5T. We have measured ratio of grey matter to white matter with ^{129}Xe spectroscopy and compared with ^1H measurement. We have developed uptake model to determine the measurement error in the grey to white matter ratio.

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Human Lung MR Imaging using Naturally-Abundant ^{129}Xe with optimised 3D SSFP

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Introduction: To date, MRI of pulmonary ventilation with the hyperpolarised (HP) noble gases ^3He and ^{129}Xe has required ~ 200 mL of ^3He or ~ 500 mL of isotopically-enriched (EN) Xe (86% ^{129}Xe) to achieve sufficient image quality for clinical interpretation. However, these gases are expensive; \$850 and \$170 per litre of ^3He and EN Xe, respectively. Naturally-abundant (NA) Xe (26% ^{129}Xe) may present an economically-attractive alternative (\$30 per litre) for routine imaging. To achieve maximal image quality for diagnostic lung imaging with NA Xe, careful utilisation of the available MR signal enhancement (hyperpolarisation) is necessary with pulse sequence optimisation. Steady-state free precession (SSFP) sequences can provide enhanced SNR in lung imaging with HP gases by recycling transverse magnetisation subject to the constraints of flip angle and diffusional dephasing [1].

Purpose: To optimise the MR acquisition process for lung imaging with HP ^{129}Xe , exploiting 3D SSFP and spoiled gradient echo (SPGR) pulse sequences in order to demonstrate the potential of NA Xe gas as a scalable, cost-effective contrast agent for imaging of pulmonary ventilation in humans.

Methods: MR imaging was performed on a healthy smoker with mild obstructive lung disease at two clinically-relevant field strengths (1.5 T and 3 T). Custom-built, flexible, transmit-receive quadrature vest coils (Clinical MR Solutions, Brookfield, WI)

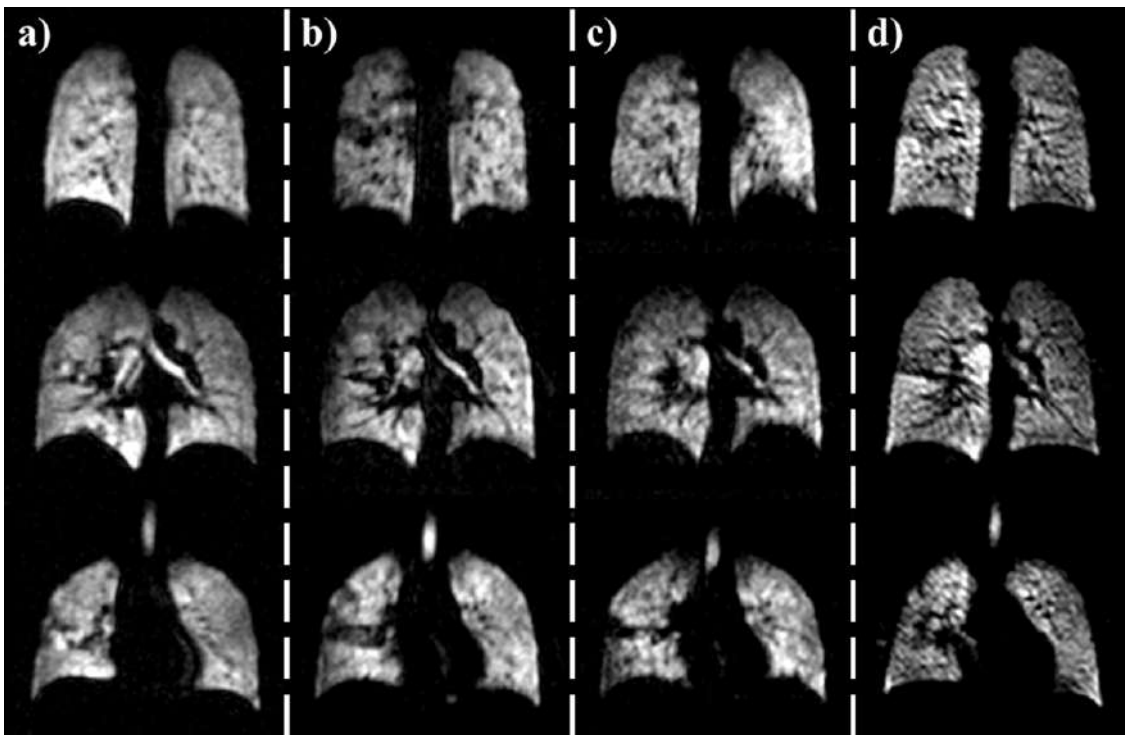


Figure 1: Selected coronal MR image slices from a healthy smoker after inhalation of a) 100 mL HP ^3He , b) 400 mL EN Xe (86% HP ^{129}Xe) and c) 1 L NA Xe (26% HP ^{129}Xe), acquired at 1.5 T with a 3D SSFP pulse sequence. Shown in d) are the corresponding slices from the same subject, obtained using a 3D SPGR pulse sequence at the field strength of 3 T.

were used to detect MR signals at the Larmor frequency of ^{129}Xe ; 17.7 MHz (1.5 T) and 35.3 MHz (3 T). NA ^{129}Xe gas (Linde Group, UK) was polarised to 30 - 60% using an in-house, regulatory-approved polariser [2]. The subject inhaled 1 L of NA HP Xe gas from a Tedlar bag and full-lung coverage MR scans were performed. 3D MR pulse sequences were employed to minimise the acquisition echo time. At 1.5 T, a 3D SSFP sequence was optimised for excitation flip angle by measuring the k-space filter from the HP ^{129}Xe signal decay across the two phase encoding dimensions (k_y and k_z) for different input flip angles [1]; a 9° flip angle resulted in a k-space filter corresponding to consumption of almost all available signal enhancement during the image acquisition. Sequence parameters were as follows: field-of-view (FOV), 40 cm; phase FOV, 0.8; 20 effective coronal slices; 0 slice gap; in-plane resolution, 96 x 96; slice thickness, 10 mm; echo/repetition time, TE/TR = 2.1/6.4 ms; receiver bandwidth, ± 8 kHz; total breath-hold, 13 sec. At 3T, a 3D SPGR sequence was implemented with the following parameters: FOV, number of slices and slice thickness as above; in-plane resolution, 100 x 100; TE/TR = 2.5/10.0 ms; receiver bandwidth, ± 7.5 kHz; total breath-hold, 16 sec. For comparison with NA Xe images, EN Xe and ^3He 3D SSFP lung imaging was performed at 1.5 T with inhaled gas mixtures of 400 mL EN Xe (86% ^{129}Xe polarised to 30 – 60%) and 100 mL HP ^3He (polarised to $\sim 25\%$), balanced to 1 L with 600 mL and 900 mL of N_2 gas, respectively.

Results & Discussion: All acquired lung MR images were of diagnostic quality, with SNRs of between 20 and 40. The high SNR permitted identification of small ventilation defects in the lungs of the healthy smoker. NA ^{129}Xe images were of comparable SNR to those obtained using modest doses of EN HP ^{129}Xe and HP ^3He (see Figure 1); i.e. for a considerably reduced cost per scan, there was no loss in diagnostic information. The similar SNR of 3D SSFP imaging at 1.5 T and 3D SPGR imaging at 3 T is promising for NA Xe lung imaging; at fixed field strength, improved SNR may be attained with SSFP versus SPGR sequences [1], whereas for the same pulse sequence, higher SNR may be available at 3 T [3], in line with that seen previously. Little / no observation of characteristic off-resonant banding or cardiac motion artefacts is also encouraging.

Conclusion: Careful optimisation of MR pulse sequences, coupled with advances in polarisation technology, can facilitate acquisition of images of pulmonary ventilation of diagnostic quality, using relatively inexpensive (\sim \$30 per scan), readily-available NA xenon gas.

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Noise-triggered NMR maser bursts in HP liquid ^3He

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In hyperpolarised liquids, the combination of a large negative spin temperature and strong radiation damping (RD) leads to the spontaneous emission of multiple RF signal bursts (instead of a single one) with asymmetric envelopes (unlike the conventional NMR maser burst). In dissolved laser-polarised Xe, the RF bursts exhibit very complex temporal and spectral features [1]. In laser-polarised He mixtures, no such chaotic behaviour is observed in experiments or simulations [2]. The succession of bursts can be explained by the competition between a RD-driven growth of the transverse component and a distant dipolar field (DDF)-induced development of inhomogeneous magnetisation patterns, which de-stabilises the precession and quenches the RF emission before spin temperature changes sign.

We report on a study aiming at a quantitative description of the onset of the RF bursts, with and without DDF, in the case where they are triggered by RF noise. Revisiting and extending prior work [3,4], we have developed a comprehensive theoretical model to account for the RF-driven random fluctuations of the average magnetisation and for its temporal evolution due to RD, B_0 field inhomogeneity, and/or DDF. We have used computer lattice simulations to probe their individual and combined contributions. A systematic experimental investigation has been performed at low field in condensed hyperpolarised ^3He - ^4He mixtures with well-controlled initial magnetisation state, adjustable radiation damping rate, and variable RF noise level. The statistics of the onset of observed RF bursts are in good agreement with the expectations. This work provides tools to interpret the irregular time delays reported in Ref. [1].

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Talks in Working Group 5
Synthetic Chemistry - Physics Interface in
Hyperpolarization Methodology

Organized by

Patrick Berthault, Bela Bode

Towards Higher Efficiency & Better Resolution in Dynamic Nuclear Polarization Enhanced Solid-State NMR

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Dynamic Nuclear Polarization (DNP) increases sensitivity of NMR by several orders of magnitude. The method exploits the transfer of large initial Boltzmann polarization of electron spins to those of neighboring nuclei. Theoretical nuclear signal enhancements of $(\gamma_e/\gamma_I) \sim 660$ can be obtained for ^1H nuclei, which could result up to a remarkable $\sim 10^{5-6}$ reduction in NMR experimental time. In practice, at 9.4 T, DNP enhancements are obtained lower much than the theoretical maximum, between 30-200. New approaches to increase the efficiency of DNP hyperpolarization will be explained by utilizing deuteration.

Moreover, the optimized way of biological sample preparation, tuning back-exchange ratio in deuterated protein preparations, and optimum DNP experimental temperatures will be summarized for achieving resolution and sensitivity. Particularly, high-temperature DNP NMR experiments performed at elevated temperatures of $\sim 180\text{-}200$ K rather than 100 K, will be discussed, which is a promising way of obtaining better resolution sufficient for structural studies of proteins via DNP.

Toward hyperpolarization of nuclear spins on diamond surfaces

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Nitrogen vacancy (NV) centers in diamond can be optically polarized by green laser light to almost 100% at room temperature. It has recently been shown that this polarization can be effectively transferred to nearby ^{14}N , ^{15}N and ^{13}C nuclear spins within the diamond crystal. Transfer of polarization to nuclear spins outside the diamond, as required for DNP of arbitrary molecules on the diamond surface, remains a challenge. In this talk we show detection of several nuclear spin species on the surface of a diamond chip by single, shallow NV centers, which is the first step toward DNP of surface molecules.

Ultrafast Z-Spectroscopy for Detection of ^{129}Xe NMR-Based Sensors

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^{129}Xe biosensors have been demonstrated to provide sensitive probes of biological events. Very sensitive detection thresholds can be reached with the HyperCEST approach¹. With hyperpolarized species it is often difficult to maintain a stable level of magnetization over consecutive experiments, which renders their detection at the trace level cumbersome, even when combined with chemical exchange saturation transfer (CEST). We report herein the use of ultrafast Z-spectroscopy (UFZ)² as a powerful means to detect low concentrations of ^{129}Xe NMR-based sensors in a single shot. This experiment enables a multiplexed detection of several sensors, as well as extraction of the exchange buildup rate constant in a single-shot fashion³.

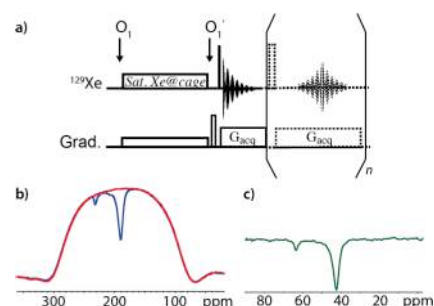


Fig. 1: (a) ^{129}Xe UFZ pulse sequence. (b) Raw data, (c) HyperCEST asymmetry curve from one-shot measurement of a mixture of cryptophanes.

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The importance of polarizing agents and the chemical environment in MAS DNP

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Polarizing agents – which provide the electron spin polarization being transferred to nuclear spins – play a crucial role in the development and application of dynamic nuclear polarization (DNP).^[1] In most cases the samples to be investigated are diamagnetic; thus, the polarizing agent (PA) has to be extrinsically added to the sample. Depending on the nature of the analyte, the matrix it is situated in, as well as the polarizing agent itself, several scenarios have to be considered. In one case both the analyte and PA are homogeneously dispersed in a glass forming solvent,^[2] or the analyte can be situated in a different phase than the PA.^[3] In any case, the ability of the solvent to form an amorphous matrix upon freezing is of crucial importance in order to prevent the phase separation of the PA.^[4] Besides using typical glass-forming mixtures, alternative approaches like sedimentation by ultracentrifugation or fast MAS can be utilized to achieve this goal.^[5]

Spin interactions between individual radical centers are a crucial requirement for efficient cross effect DNP. Symmetric bis-TEMPO biradicals have been extraordinarily successful for ¹H DNP.^[6] Even though attempts to synthesize water-soluble non-symmetrical biradicals constituent of one or two narrow EPR-line moieties have proven extremely challenging, mixtures of the respective monoradicals have shown to be highly efficient, especially for direct DNP of nuclei with a small gyromagnetic ratio (*e.g.* ¹³C, ²H).^[7] Finally, paramagnetic metal ions can act as PA, either in the form of a complex ion dispersed in an aqueous solution,^[8] or as dopant incorporated into a crystalline inorganic host material.^[9] Furthermore, it has been shown that endogenous radical centers can be used as PA for DNP.^[10] This is especially interesting since the incorporation of paramagnetic metal ions into biomolecules might lead to new, intriguing possibilities.

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Diffusion of polarizing agents into nanostructured materials: a critical factor for DNP-enhanced NMR experiments

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We have shown recently that Dynamic Nuclear Polarization (DNP) can enhance the sensitivity of solid-state NMR experiments on nanostructured materials, including mesoporous silica^{1,2} and microporous metal-organic frameworks (MOFs).³ For these DNP-NMR experiments, porous materials were impregnated with a solution containing stable nitroxide biradicals, which act as polarizing agents.

We demonstrate here that the diffusion and the adsorption of polarizing agents are critical factors for DNP- NMR experiments on micro- and meso-porous materials. We also show that these phenomena can be probed using EPR and DNP-NMR spectroscopies. For instance, 2D EPR imaging was employed to control the impregnation of mesoporous silica by biradical solutions.¹ EPR measurements also indicate a higher electron concentration in mesoporous silica than in the solution, which suggests the adsorption of TOTAPOL molecules onto the silica surface. Conversely the presence of surfactant molecules within the pores of mesoporous silica inhibits the access of biradicals to the mesopores, relegating them to the interparticle voids.² This exclusion of TOTAPOL from mesopores was proven using EPR spectroscopy and a quantitative analysis of DNP signal enhancements.

In microporous MOFs, the exchange between radicals in solution and adsorbed onto the micropores is slow enough to detect two distinct EPR signals for these species.³ Therefore, the evolution of EPR signals allows monitoring the kinetics of the adsorption of biradicals on the large cavities of MIL-100(Al). This adsorption was confirmed by an analysis of the DNP enhancement using 1H spin diffusion models.

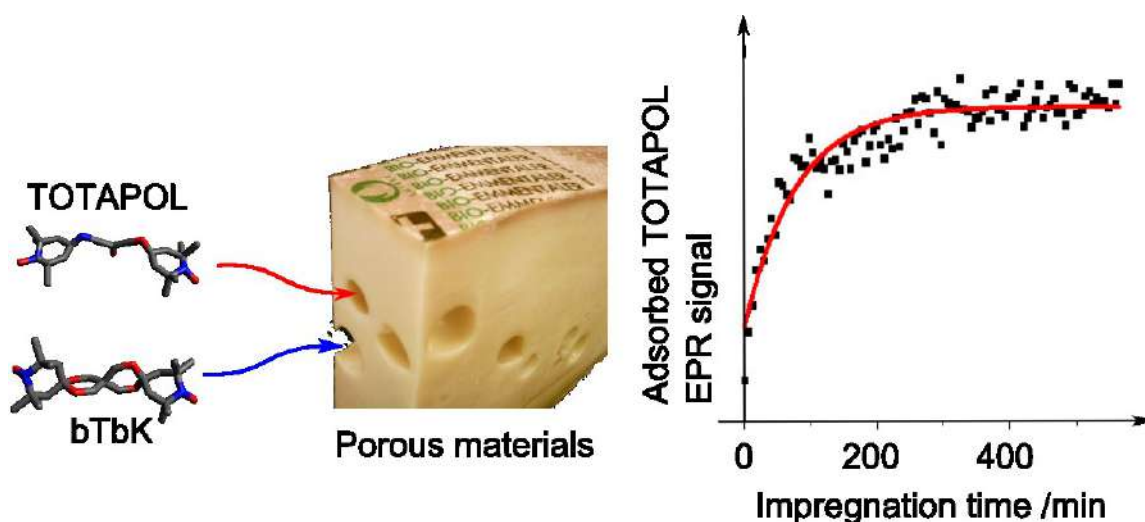


Figure: DNP-NMR and EPR spectroscopies allow monitoring radical diffusion in porous materials.

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Increasing water-solubility of radicals for DNP using dendrimer chemistry

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Dynamic nuclear polarization (DNP) is currently one of the most efficient methods to increase NMR signal intensities, where polarization is transferred from a paramagnetic molecule to the nuclei of interest. Several new radicals have been prepared in recent years. bTbk is a biradical that has given the largest enhancement thus far^[1], but a major problem with this radical, as with many others, is its limited solubility in aqueous solutions. This is the major hurdle of using bTbk for DNP experiment of biological systems.^[2]

We are currently working on a strategy to attach water-soluble functional groups to nitroxide radicals by using a dendrimer approach, specifically thiophosphonate dendrimers that can be synthesized using well-known phosphoramidite chemistry.^[3] We have incorporated hydroxyl groups into nitroxide radicals that can be used for this thiophosphonate dendrimer chemistry. This approach can be used to link water-soluble functional groups to nitroxide radicals to enhance their aqueous solubility. The relaxation time of nitroxide radicals should also increase by increasing the molecular weight through dendrimer derivatization.^[4]

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Effects of field modulation on rate of growth of polarization at very high B_0/T

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High levels of nuclear spin polarization can, in principle, be achieved simply by exposure to low temperature and high magnetic field. This is known as the brute-force method. However, the long time required for the polarization to approach thermal equilibrium poses problems. We have previously shown that these problems can be addressed using copper and cupric oxide nanoparticles as low temperature (millikelvin) relaxation agents. For example, in experiments at 14 T and 15mK conducted on a 50/50 water/glycerol solution that included 2M [^{13}C] sodium acetate, we showed that, in the presence of copper nanoparticles (1:4 volume ratio of nanoparticles to solution), the ^{13}C $T_{1/2}$ value for growth towards the equilibrium polarization of 23% was about 60 hours, whereas with aluminium nanoparticles the ^{13}C $T_{1/2}$ was at least one year (1). Here, we show that the rate of growth of polarization can be further enhanced at very high values of B_0/T by modulating the magnetic field B_0 . Experiments were undertaken at 9.74 T and 20 mK on a 50/50 water/glycerol solution containing 4M [^{13}C] sodium acetate in the presence of copper nanoparticles (volume ratio 1:8 of nanoparticles to solution). The magnetic field B_0 was modulated by ramping to either 8T or 11.48 T at rates of up to 0.3 T/min before returning to resonance at 9.74 T and re-measuring the polarization. Depending upon the starting conditions, the initial rate of growth of ^{13}C polarization could be enhanced by as much as a factor of 6 compared with its growth in the absence of ramping. Experiments are currently in progress to assess the various factors that could influence the effects of modulation. These factors include the extent and rate at which the field is ramped, the polarization state of the other nuclei within the sample, as well as the steady state temperature and magnetic field.

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Polyradical species involving trityl radicals

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Polyradical species obtained by chemically linking nitroxide radicals have shown superior capacity for solid-state DNP. Trityl radicals are extensively used for direct polarization of heteronuclei in dissolution dynamic nuclear polarization (DNP). Chlorinated trityl radicals have also been shown to provide good relative polarization efficiencies.

In this communication we shall present recent and ongoing work of the group, which involves polyradical species with trityl radicals of different types. One of the examples is a novel diradical containing a chlorinated trityl that shows very efficient DNP properties in terms of absolute polarization achieved and polarization rate.

The second example involves supramolecular polyradical species formed by the widely used OX63 and Finland radicals. The Finland and OX63 radicals, of similar structure, differ strongly on their polarization efficiency. Finland has a high tendency to form oligomers in aqueous solution even at low concentration. OX63 has a lower tendency to oligomerize alone but forms dimers by encapsulation of proper guests. The supramolecular properties of these classical trityl radicals have been confirmed by EPR, mass-spectrometry and are consistent with the predictions of DFT calculations. The presence of these species gives rise and explains the unusual DNP properties, reported in a previous COST meeting.

Water soluble spacers for biradicals

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Using biradicals instead of monoradicals as polarizing agents can yield significantly larger dynamic nuclear polarization (DNP) [1]. This effect depends to a great extent on the distance and relative orientation of the two spin labels. For most biological applications water solubility of the polarizing agent is indispensable. Therefore water-soluble biradicals with well-defined intraradical distance and orientation are of high interest as polarizing agents for the DNP/NMR study on biological systems.

Monodisperse oligo(*para*-phenyleneethynylene)s (OPPEs) are excellent spacers for the biradicals because of their rodlike shape and well known stiffness [2]. The synthesis of water-soluble OPPEs is a challenge because the polar, water solubilizing side chains interfere with the reactions used for the construction of the spacer's backbone and especially hamper isolation of reaction products.

Here we report on an approach in which first the nonpolar spacer backbone is synthesized and postsynthetically the polar side chains are attached. The backbone synthesis makes use of orthogonal alkyne protecting groups and of polar alkyne protecting groups for tagging target molecules. The polar side chains are attached via click chemistry. On this way we avoided the above mentioned difficulties associated with polar side chains and prepared water soluble biradicals with nitroxyl as well as Gd³⁺-complexes as spin labels and spin-spin distance of 2-11 nm. Moreover, this approach offers easy adjustability of the solubility and functionality of spacers and therefore of biradicals to specific requirements, e.g. solubility in lipid bilayers.

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Mesostructured Hybrid Silica Materials Characterization and Use as Polarization Matrices

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In recent years, we have established the application of Solid State Dynamic Nuclear Polarization (DNP) NMR to investigate the structure of surface sites in mesoporous hybrid silica materials. This technique uses a polarization transfer from polarization agents, in high field DNP NMR mainly biradicals in a frozen matrix.[1]

Here, we present the synthesis, in the presence of structure directing agent, of a mesostructured hybrid silica material containing organic functionalities regularly distributed along the pore channels. The organic functionality is then used as a platform to incorporate different radicals, which are distributed homogeneously within the material porous network according to EPR. The use of these materials in high field MAS DNP NMR as a polarization matrices shows enhancements up to 45 for small organic molecules while the same radicals in solution or grafted on similar silica materials give significantly lower enhancements. In dissolution DNP, the polarized solution shows good enhancement and is easy to separate from the material by filtration thus opening new approach in imaging technology.[2]

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Posters

Ultrafast multidimensional Laplace NMR

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NMR relaxation and diffusion experiments can provide versatile information about the dynamics and structure of substances such as proteins, polymers, porous media etc. They are particularly useful in systems which lack chemical resolution. In such a case the different components may still be separable by their diffusion coefficients or relaxation rates. Since the relaxation and diffusion data consists of exponentially decaying components, the processing requires a Laplace inversion, and consequently these methods can be referred as Laplace NMR. Like in traditional NMR spectroscopy, the resolution and information content of Laplace NMR can be increased by the multidimensional approach [1].

Similarly as in traditional multidimensional NMR, long experimental time restricts the applicability of multidimensional Laplace NMR in the study of fast processes. A wait time of about T_1 is necessary before repeating the experiment with a different evolution time. Therefore, the acquisition of full multidimensional data may take from minutes to hours. Furthermore, conventional multidimensional experiments prevent using hyperpolarized substances for signal amplification, because the hyperpolarization step should be repeated several times. This would be far too time-consuming, and polarization degree might vary significantly.

We describe a novel strategy which enables ultrafast, single scan multidimensional Laplace NMR. The method is based on spatial encoding of the indirect relaxation or diffusion information similarly like in ultrafast multidimensional NMR spectroscopy [2]. For example, single scan T_1 - T_2 correlation experiment [3] consists of successive inversion recovery (IR) and CPMG blocks, as in the conventional experiment, but in the present case all the different T_1 evolution times undergo a multiplexing process within layers of the sample perpendicular to the axis of a sample tube like in single-scan IR approach published by Loening et al. [4]. CPMG part includes also an imaging gradient in order to measure 1D profile of the sample. Ultrafast D- T_2 sequence, in turn, includes spatial encoding of diffusion data similarly as in 1D DOSY [5] experiment, followed by a CPMG block for T_2 encoding. The method is applicable to hyperpolarized systems, because it does not require multiple repetitions for the acquisition of the whole multidimensional data matrix. Chemical shift information can be also included to the measurement data.

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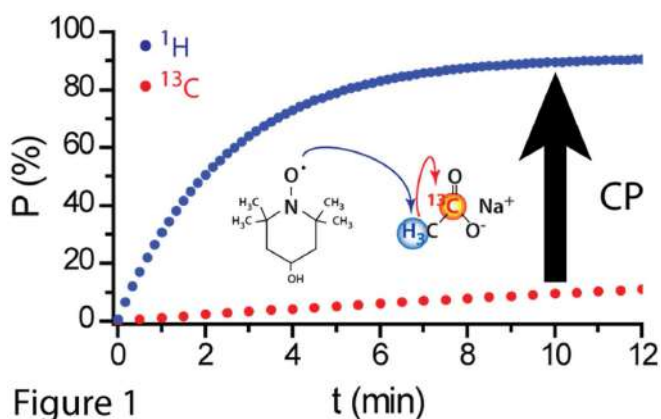
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Cross-Polarization from ^1H to ^{13}C for Dissolution-DNP at 6.7 T and 1.2 K

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and Geoffrey Bodenhausen^{1,4,5,6}

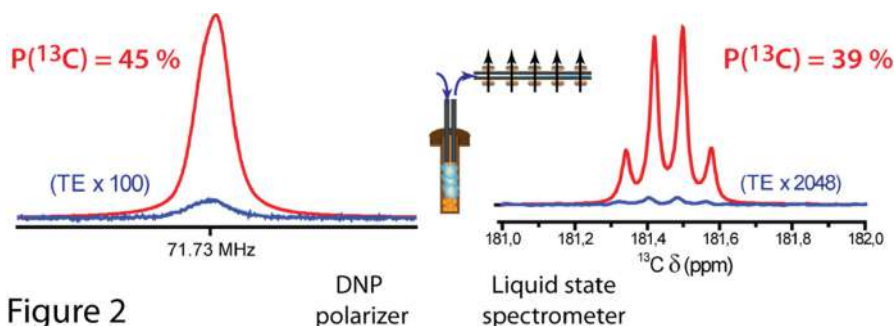
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Dissolution DNP [1] is commonly performed at moderate magnetic fields (typically $B_0 = 3.35$ T) and low temperatures (often 1.2 K) with polarizing agents with narrow ESR lines such as the triarylmethyl radical (TAM) OX63. It was recently demonstrated that a direct ^{13}C polarization up to $P(^{13}\text{C}) = 36\%$ could be achieved with TAM below 1 K [2]. A limiting factor is the slow build-up



with a long time constant $\tau_{\text{DNP}}(^{13}\text{C}) > 2000$ s. Because build-up time constants tend to become even longer at higher magnetic fields, increasing the magnetic field to improve the ^{13}C magnetization turned out to be disappointing.[4,5] Nitroxyl radicals with broad ESR lines such as TEMPOL are known to polarize ^{13}C with faster build up time constants than TAM. We demonstrated [3] that by doubling the microwave frequency and the field from $B_0 = 3.35$ to 6.7 T, the directly enhanced ^{13}C polarization increases from $P(^{13}\text{C}) = 10$ to 35 %. Moreover, TEMPO turns out to be much more efficient than TAM to polarize ^1H . A proton polarization as high as $P(^1\text{H}) = 91\%$ could be obtained with a build up time constant as short as $\tau_{\text{DNP}}(^1\text{H}) = 150$ s at $B_0 = 6.7$ T and $T = 1.2$ K [6]. This remarkably high proton polarization can be transferred to ^{13}C polarization using Hartmann- Hahn cross polarization (CP). Using a doubly tuned horizontal solenoid coil designed for CP at 1.2 K, an unprecedented ^{13}C polarization $P(^{13}\text{C}) > 70\%$ was obtained in less than 20 min [6].

This approach was made compatible with dissolution DNP [1], using a CP-DNP probe equipped with a vertical doubly tuned NMR saddle coil for ^1H and ^{13}C . After CP transfer of the ^1H polarization to ^{13}C at 1.2 K, the solid sample is rapidly dissolved and



transferred to a liquid state NMR spectrometer. Polarization losses are limited during the transfer by scavenging the radicals using Vitamin C (ascorbate) and/or by using a magnetic tunnel to sustain a field of 0.8 T during the voyage, so as to avoid a perilous trip through the 'death valley' between the two magnets where the field can be very low. In the liquid state, the polarization was determined to be $P(^{13}\text{C}) = 39\%$ [7].

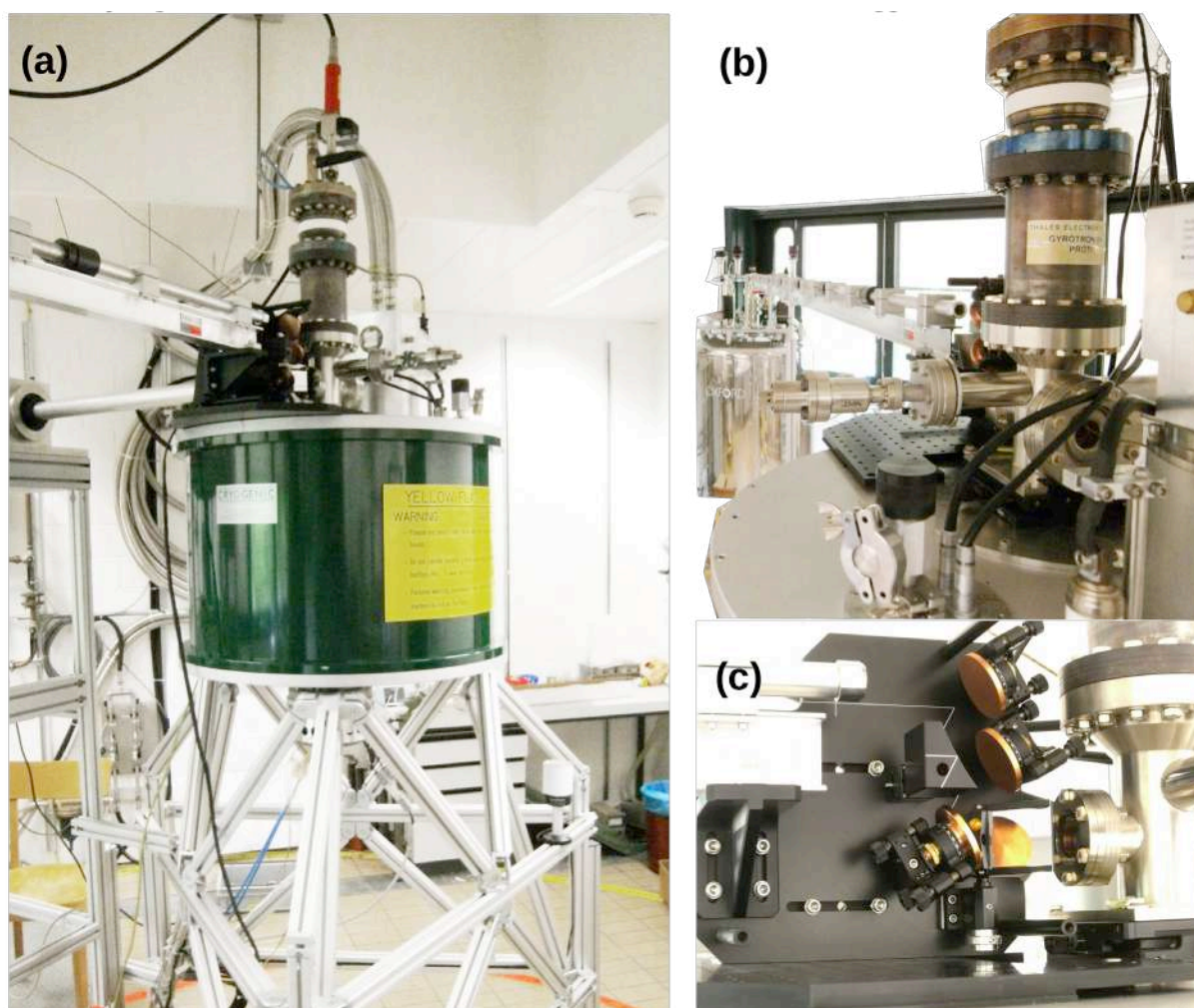
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Tailoring 260 GHz-Gyrotron Radiation for DNP and ESR Applications

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Controlling dynamic nuclear polarization (DNP) by high-intensity and high-frequency Gyrotron radiation renders possible a wealth of complementary NMR and ESR studies [1]. We present the characteristics and possible applications of a custom-designed THz-Gyrotron at the LPMN group (EPF Lausanne) which we connected to a 9.3 Tesla-NMR apparatus.



Operation modes of the electron Gyrotron (Fig. a) cover a variety of regimes for the THz radiation from stationary (constant frequency), to chaotic [2]. Our development focuses on the Gyrotron properties in stationary operating regimes with a particular emphasis on the operational characteristics relevant for DNP-NMR studies (Fig. b). We achieved herein frequency-tunability, spectral purity, as well as the selection of pulsed regime or continuous wave (CW) modes. The THz-wave polarization control is successfully implemented in the matching optical unit (MOU,

Fig. c), thus providing control over linear and circular polarization states of the THz beam.

The stationary, single-frequency regime has been extensively characterized for the nominal operating transverse mode TE_{7,2} radiating at 260 GHz [3]. In CW mode, we have demonstrated a continuous frequency tunability via the variation of the cavity magnetic field, with very-high frequency and power stability (drift $\Delta f / f < 0.01$ ppm, $\Delta P_{rf} / P_{rf} < 1\%$). Thereby, the RF output power exceeds 1.5 W, and a maximum power of 150 W has been observed.

In summary, a detailed characterization of the properties of a 260 GHz frequency-tunable Gyrotron for DNP-NMR experiment has been conducted. Full control over spin polarization of the sample's electron system will soon be achieved by the implementation of a Martin-Pupplet interferometer in the THz radiation pathway. This opens up the opportunity for in-depth DNP-NMR experiments, combining investigations of both the nuclear and electronic spin system

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Interpreting DNP results of TEMPO doped samples by a rate equation approach in the TM regime.

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Dynamic Nuclear Polarization is becoming more and more popular as highly efficient technique to enhance Nuclear Magnetic Resonance (NMR) signals by several orders of magnitude. Many impressive experimental results have been obtained in different fields (analytical, biomedical, etc.), while a widely-accepted physical description of the mechanisms underlying DNP is still missing. Recently we developed a novel theoretical approach in the thermal mixing regime (TM) based on rate equations [1-3] that overcomes several limitations of traditional approaches. The model provides theoretical interpretations for conventional experiments in samples doped with narrow width radicals (*e.g.* trityls), for example concerning the influence of the radical concentration and of gadolinium doping on the final nuclear polarization.

Focusing on broad band radicals, such as nitroxides, the experimental scenario shows some additional and different features [4-6]: (i) the existence of a unique spin temperature between different nuclear species (*i.e.* protons and carbons), (ii) a polarization enhancement on reducing the number of protons, (iii) a re-polarization of ¹³C nuclei in system with highly polarized protons when turning off microwave irradiation, (iv) a reduced effect of gadolinium and a shift of optimal polarization to higher radical concentration with respect to trityl doped samples.

In this work we will discuss the experimental results and provide a preliminary interpretation in the light of the developed rate equation approach. In particular, we will argue about the efficiency of the contact between the different thermal baths (protons – electrons, carbons – electrons, protons – lattice and electrons - lattice), highlighting how a weaker or stronger thermal contact affects the system and can or cannot explain the experimental observations.

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SABRE Hyperpolarization in Trace Analysis

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Our aim is to detect highly dilute molecules in biological fluids. For the analysis of such complex mixtures NMR spectroscopy is a powerful tool, since simultaneous measurements of all kinds of molecules is possible without extensive sample preparation. Unfortunately, its inherent low sensitivity restricts NMR typically to samples at millimolar or high micromolar concentrations.

In order to increase NMR sensitivity, we use *para*-hydrogen in a method called Signal Amplification By Reversible Exchange (SABRE). SABRE is based on the reversible interaction of *para*-hydrogen and a substrate molecule through a metallo-organic complex¹. Using a co-substrate approach it is possible to detect molecules in the low micromolar to nanomolar range². Here we show a quantitative application of SABRE for dilute substrates in artificial mixtures.

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High field Overhauser DNP Experiments on oriented fluid Lipid Bilayers using a Stripline/Fabry Perot Double Resonance Structure

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DNP-enhanced solid-state NMR mainly based on the cross effect and in combination with MAS has been shown to hold great potential for the study of membrane proteins. So far, such studies require experiments at low temperatures around 100 K and the mechanical requirements for magic angle sample spinning are not easily compatible with a microwave resonator structure. Furthermore, the use of DNP for oriented solid-state on aligned membrane systems is just emerging (1).

Here, we demonstrate as a proof of concept, that Overhauser-DNP enhanced NMR spectra on oriented lipid bilayers can be obtained under room temperature conditions. Experiments were carried out using a homebuilt 400 MHz/263 GHz DNP-NMR spectrometer equipped with a RF/microwave double resonance structure. Such a structure is necessary to avoid excessive heating of the liquid sample at room temperature. Instead of a RF coil, a stripline structure is used coupled with Fabry-Perot microwave resonator (2). Different lipid bilayers were directly aligned on the stripline with the membrane normal parallel to B₀. Different mono- and biradicals were tested and a DNP enhancement of lipid proton acyl chain resonances of up to -15 was observed. DNP on membrane embedded ion channels was also explored. The unexpected high enhancements observed at high magnetic field might be caused by fast local dynamics between the lipid membranes and the radicals (3).

Our data show that DNP at RT on oriented lipid bilayers is possible and that the presented hardware offers a promising platform for further developments towards DNP-enhanced oriented-solid-state NMR on non-frozen membrane protein samples.

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The ^{13}C solid DNP Mechanisms with Perchlorotriphenylmethyl Radicals – the Role of $^{35,37}\text{Cl}$

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The microwave frequency swept DNP enhancement, referred to as the DNP spectrum, reveals the underlying DNP mechanisms that are, in turn, highly dependent on the EPR lineshape of the polarizing radical. Here we focus on two chlorinated trityl radicals that at 95 GHz feature axially symmetric powder patterns, the width of which are narrower than those of TEMPOL or TOTAPOL but are broader than that of triyl, OX63. The static DNP lineshapes of these radicals, commonly used in DNP, were analyzed in terms of a superposition of a basic SE (solid effect)- and CE- (cross effect)- DNP lineshapes, with their relative contributions as a fit parameter.¹⁻³ To substantiate the generality of this approach and further investigate an earlier suggestion that a $^{35,37}\text{Cl}$ - ^{13}C polarization transfer pathway,⁴⁻⁵ termed “hetero-nuclear assisted DNP”, may be in effect in the chlorinated radicals we measured the static ^{13}C -glycerol DNP spectra these radicals. Solutions of ca. 10 mM of the two radicals were used and measurements were carried out as a function of temperature (10-50 K) and microwave power. Analysis of the DNP lineshapes was first done in terms of the SE/CE superposition model calculated assuming a direct e- ^{13}C polarization transfer. The CE was found to prevail at the high temperature range (40-50K), whereas at the low temperature end (10-20K) the SE dominates, as it observed earlier for ^{13}C DNP with trityl and ^1H DNP with TEMPOL and TOTAPOL¹⁻³, indicating that this is rather general behavior. Furthermore, it was found that at low temperatures it is possible to suppress the SE and increase the CE contribution by merely lowering the microwave power. While this analysis gave a good agreement between experimental and calculated lineshapes when the CE dominates, some significant discrepancies were observed at low temperatures, where the SE dominates. We show that by explicitly taking into account the presence of $^{35/37}\text{Cl}$ nuclei through a e- $^{35,37}\text{Cl}$ - ^{13}C polarization pathway in the SE-DNP lineshape calculations we can improve the fit significantly, thus supporting the existence of the “hetero-nuclear assisted DNP” pathway.

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DNP using photo-excited triplet states: above 70% proton spin polarization at moderate magnetic field and temperature

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The gist of Dynamic Nuclear Polarization (DNP) is to exploit the higher polarization of an electron spin system by transferring it to the nuclear spin system by means of a microwave field. In traditional DNP the electron spins are provided by stable paramagnetic centres and polarized by cooling down to low temperature and applying a strong magnetic field.

Elaborate cryogenic equipment and superconducting magnets are avoided using short-lived photo-excited triplet states that are strongly aligned in the optical excitation process. Thus we have reached a record polarization of 71% of the proton spins in a pentacene doped naphthalene single crystal at a field of 0.36 T using a simple helium flow cryostat for cooling [1].

The short triplet lifetime of a few tens of microseconds requires a fast polarization transfer. The traditional CW microwave irradiation, used for DNP via thermal mixing or the solid effect, is too slow and we use the pulsed DNP methods Nuclear Orientation Via Electron Spin Locking (NOVEL) and the Integrated Solid Effect (ISE). These techniques use strong microwave fields allowing a fast polarization transfer under the Hartmann-Hahn condition. Then, contrary to traditional DNP, the polarization transfer is coherent and its description is fundamentally different [2,3].

We built a versatile experimental setup to perform and optimize pulsed DNP using photo-excited triplet states [4]. It operates at X-band and 4 - 300 K and is also used in neutron spin filter experiments. With this apparatus we reached the high proton spin polarizations mentioned above and checked the theory of the polarization transfer in ISE. An excellent quantitative agreement is found.

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Use of hyperpolarized ^{129}Xe Nuclear Magnetic Resonance Spectroscopy for the analysis of modified diatomite

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Diatomite is a mineral that can be found in natural sediments. It is classified as a siliceous sedimentary rock, product of the accumulation and compaction of fossilized remains of diatoms over geological time scales. It is composed of amorphous silica and has several interesting properties such as high porosity, strong adsorbability, good thermal resistance and chemical inertness [1,2].

The physical and chemical behavior of diatomite is influenced by the presence of hydroxyl groups over its surface (i.e. silanols). Modification of diatomite can be achieved by reactions over its silanols under inert atmosphere. The extent of modification will depend in the availability of the silanols: the more the silanols are isolated, the higher the modification that can be achieved. A different amount of hydroxyl isolation can be obtained by thermal treatment to the diatomite prior to modification [2].

Diatomite samples treated at different temperatures were modified by silylation using trimethylchlorosilane in dry toluene under $\text{N}_2(\text{g})$ -atmosphere. The resulting materials (methylated-diatomites) have been characterized by infrared spectroscopy, scanning electron microscopy, X-ray diffraction and contact angle measurements.

Here, we present a study of the methylated-diatomites by hyperpolarized ^{129}Xe Nuclear Magnetic Resonance spectroscopy (HP- ^{129}Xe NMR). HP- ^{129}Xe NMR is a powerful technique to study porous materials. The method presents a high sensitivity, allowing to work in low concentrations of Xe where the contribution of the Xe-Xe interactions is negligible and the observed results are due to the interactions between the Xe atoms and the surface of the material tested [3,4].

We use HP- ^{129}Xe NMR to study differently pretreated and surface modified diatomite samples. Those studies include continuous flow HP-Xe- ^{129}Xe NMR measurements as well VT-NMR- and EXSY-experiments.

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Spin mixing at level anti-crossings in the rotating frame makes high-field SABRE feasible

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A new technique is proposed to carry out Signal Amplification By Reversible Exchange (SABRE) experiments at high magnetic field. SABRE is a method, which utilizes spin order transfer from para-hydrogen to the spins of a substrate in transient complexes with suitable catalysts. Such a transfer of spin order is efficient at low magnetic fields, notably, at Level Anti-Crossing (LAC) regions. In this work, it is demonstrated that LAC conditions can also be fulfilled in the rotating reference frame under the action of an RF-field. Spin mixing at such LACs allows one to polarize substrates at high fields as well; the achievable NMR enhancements are around 50 for the ortho-protons of the substrate pyridine and around 300 for H₂ and substrate in the active complex with catalyst.

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The Haupt Effect for ^{12}C and ^{13}C Methyl Groups

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Over the past 50 years, many different techniques have been developed in order to hyperpolarize target molecules for various applications like structure determination or in vivo imaging. A potential hyperpolarization method is the Haupt effect where the polarization generated in tunneling methyl groups [1] within a target molecule can be used without utilizing additional substrates like radicals as done for DNP [2,3]. Since CH_3 groups occur frequently in biological systems this hyperpolarization technique might stimulate interesting experiments on various compounds and molecules.

At low temperatures, the motion of the methyl group is more accurately described by a tunneling motion than as a classical jump process. A sensitivity gain for CH_3 groups when cooling them below 5 K followed by a rapid temperature-jump to higher temperature was already reported in the 1970s and termed the 'Haupt-Effect' [1]. Aside from a potential use as a hyperpolarization technique the motion of this rotor is also a prime example of a system undergoing a transition from a classical to a quantum mechanical regime, therefore posing a model system to answer more fundamental questions.

Here we will show the latest work done in our laboratory on the Haupt effect. Data from low temperature measurements (3-12 K) on powders from ^{13}C -labeled as well as natural abundant samples will be presented. The time dependence of the build up of the low-temperature ground state that has the same form as the homonuclear isotropic J -coupling Hamiltonian was indirectly measured and can be explained from a relaxation model. We have also analysed temperature-jump experiments in powders and single crystals of $^{12}\text{CH}_3$ and $^{13}\text{CH}_3$ groups in terms of a simple longitudinal dipolar relaxation model of isolated methyl groups. The model uses a classical or tunneling model for the modulation of the dipolar coupling by the motion of the methyl group.

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Investigation of the dynamic nuclear polarization transfer mechanism in molecular and crystalline model systems

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Dynamic nuclear polarization (DNP) has become an important tool to overcome the sensitivity issue of solid-state NMR and has been shown to be especially useful when studying nuclei with inherently low sensitivity. Generally, radicals which are dissolved in a glass forming solvent act as the source of electron polarization. However, in systems like inorganic crystals the use of organic radicals (e.g., TOTAPOL, bTbK) is not feasible. Nevertheless, these materials often can be prepared with paramagnetic dopants without significantly affecting the host structure.

Although DNP is widely applied, the transfer mechanism is not fully understood. Quantum mechanical models can only be applied for small systems of a few spins, whereas experiments often observe the collective behavior of several hundreds to thousands nuclei per electron spin. Furthermore, experiments in disordered lattices only reveal an average behavior of all molecular orientations and therefore are unsuited for investigation of theoretically proposed orientationally dependent effects.

We present several approaches allowing the investigation of the above mentioned effects using disordered of molecular model systems as well as ordered systems in single- and polycrystalline form. Experiments are performed using a combination of multi-frequency EPR, solid-state NMR, as well as DNP. The results will be interpreted in the light of current theoretical models and findings in applied DNP experiments.

Explaining dynamic behavior of in situ SABRE by level anti crossing

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As demonstrated before^{[1][2]} Level anti crossing (LAC) can provide valuable qualitative insight into the magnetic field dependencies of Polarization transfer in SABRE experiments. This former work was expanded to provide a qualitative and quantitative understanding of the time dependent dynamics which are encountered in the investigation of the recently described^[3] continuous Re-Hyperpolarization using in situ SABRE. Although Full-Hamiltonian simulations are the most straightforward approach in describing the time evolution of the in situ SABRE experiments^[4] they can be time-consuming in terms of computation and their physical interpretation might not be obvious on first sight.

Instead LAC can be used to describe the time evolution and dynamic system properties such as time-at-catalyst t_c and maximum polarization transfer in a more accessible way. In addition the time and field dependencies which were reported before^[3] can be calculated more efficiently. This is done by determining analytical expressions for each LAC which approximate the time evolution of the full Hamiltonian with a deviation of less than 1 %. With this we present a previously not reported method to easily derive analytic expressions for the time evolution of a four-spin system describing SABRE experiments.

We identified five previously non-Interacting eigenstates of the Hamiltonian as well as their energies and coupling terms. These form three LAC's which are sufficient to describe the previously reported polarization Pattern. Figure 3 and 4 show the LAC calculation and the full Hamiltonian calculations respectively. For example the time evolution of the density matrix at $B_0 = 0.01$ T can be described by the evolution of the two relevant populations.

$$a^2(t)|T_+, T_- \rangle \langle T_-, T_+| + b^2(t)|S, S \rangle \langle S, S| \quad (1)$$

with $a^2(t) = \frac{4|W_{12}|^2}{4|W_{12}|^2 + (E_1 - E_2)^2} \cdot \sin^2\left(\sqrt{4|W_{12}|^2 + (E_1 - E_2)^2} \frac{t}{2}\right)$, $b^2(t) = 1 - a^2(t)$
where $E_1 = -\frac{3}{2}\pi(J_{12} + J_{34})$, $E_2 = 2\pi\gamma B_0(\delta_{1/2} - \delta_{3/4}) + \frac{1}{2}\pi(J_{12} + J_{34} - J_{13} + J_{14} + J_{23})$
and $W_{12} = -\frac{1}{2}\pi(J_{13} - J_{14} - J_{23})$. In this equation δ_i is the chemical shift of nucleus i and J_{ij} the scalar coupling constant. From this equation it becomes clear, that maximum polarization transfer is achieved when the initial populations from state $|S, S\rangle$ have been transferred to state $|T_+, T_-\rangle$.

Thus a maximum polarization transfer of 25 % can be achieved when considering this LAC. The optimal time t_c for this transfer to occur can be obtained by maximizing the transition probability $a(t)^2$.

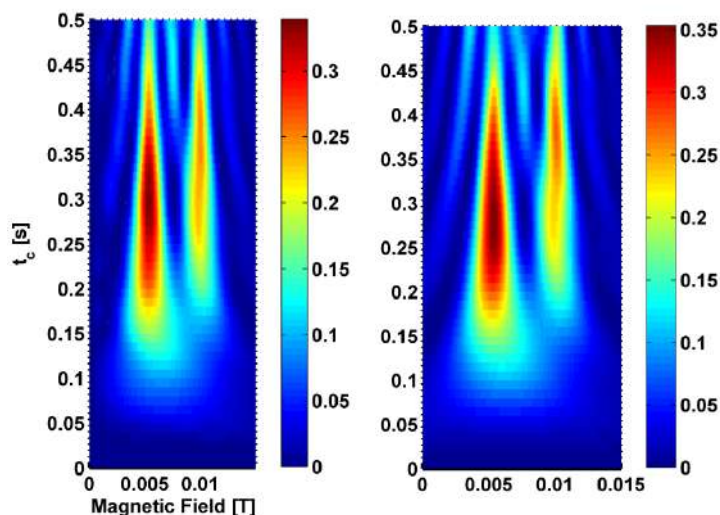


Figure 1 (left): polarization transfer pattern calculated by using three LAC's (right): transfer pattern calculated with Full-Hamiltonian simulations, the deviations are less than 1 percent.

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Liquid state DNP coupling constants for TEMPOL in acetone and DMSO from MD simulations

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The ability of the nitroxide radical TEMPOL to polarize the hydrogen spins of the solvents acetone and DMSO is explored computationally. Although the molecules of these two solvents are structurally similar, their viscosities are very different: DMSO is about 2.3 times more viscous while acetone is about 2.6 times less viscous than water. A central question therefore is whether the six-fold difference in the self-diffusion coefficients of the two liquids is sufficient to explain the differences in their DNP coupling factors with TEMPOL. Performing molecular dynamics simulations, dipolar correlation functions between spins corresponding to the unpaired electron of TEMPOL and hydrogens of acetone and DMSO were calculated [1]. The resulting spectral densities were then used to obtain the DNP coupling constants for a range of experimental frequencies. Comparing the calculated coupling factors with the analytical model of hard spherical molecules with centered spins [1,2] we conclude that diffusion alone is not sufficient to rationalize the numbers. The analytical model of spherical molecules with off-centered spins [4] is demonstrated to better predict the frequency behaviour of the DNP coupling factors, highlighting the need for good correspondence to the molecular reality.

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Enhancing nuclear polarization of a nitrogen atom trapped inside a fullerene cage with ENDOR spectroscopy - comparison between experimental data and quantum-mechanical simulations

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Atomic nitrogen trapped inside a fullerene cage (C₆₀) constitutes an interesting model system to store quantum information. The nitrogen placed in a high-symmetry site at the centre of the cage is well protected from interactions with the environment, retaining its paramagnetic properties.

Due to the highly isotropic nature of the system, the solid effect (SE) cannot be used to effectively polarize the nitrogen nuclear spin [1]. A novel method of increasing nitrogen nuclear polarization inside the cage has been proposed, based on a selective excitation of both electronic and nuclear transitions via ENDOR spectroscopy (so called ENDOR-DNP) [2,3]. In the case of ¹⁵N trapped inside C₆₀, the experimental data show a nuclear polarization build-up of up to 62% within 20 min [2].

To reveal more about the mechanisms of ENDOR-DNP, we performed full quantum-mechanical simulations of the model spin system for various different conditions including temperature, relaxation times and irradiation power. A theoretical treatment [3] has suggested that only up to a half of the thermal electron polarization can be transferred on the nuclear spins. We found that in the low temperature limit the system becomes very sensitive to the initial electron thermal polarization and in certain conditions it is possible to overcome this limitation.

Moreover, the initial data suggest that the large nuclear polarization obtained with ENDOR-DNP might be further utilized to polarize bulk nuclei by using the ¹³C spin from the fullerene's wall. Based on spin dynamics simulations, we discuss the limitations and advantages of this approach emphasising how this process can be optimized in the future.

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Overhauser DNP efficiency of different nitroxide radicals at 9.4 T

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Overhauser dynamic nuclear polarization (ODNP) can provide large signal enhancements for proton NMR in liquids [1]. This can be of specific interest for samples, where the signal intensity is limited, as for example *in-cell* NMR. In this case, experiments have to be performed at high magnetic fields to achieve chemical shift resolution, which is challenging for ODNP because of technical and physical reasons. Nevertheless we could show that signal enhancement of -14 could be achieved at 9.2 T magnetic field (400 MHz proton frequency) at room temperature for water protons using a TEMPOL nitroxide radical as polarizing agent [2]. However, in cells TEMPOL radicals get very fast reduced to diamagnetic hydroxylamine. Therefore, for ODNP “in vivo” applications, more stable nitroxide radicals have to be used. Recent studies showed that depending on the nitroxide radical structure it is possible to improve its resistance to reduction [3, 4]. In particular, reduction kinetics studies of nitroxide radicals in aqueous solutions have pointed out that the five-membered-ring 3- Carboxy-PROXYL (CP) radical presents better resistance to reduction with ascorbic acid or Glutathione compared to six-membered-ring 4 (TEMPOL) radical [3].

In this work ODNP experiments have been performed at high field (9.4 T) using different radicals in water and DMSO. Similar DNP enhancements for 3-carboxy-PROXYL radical and TEMPOL radical were obtained in both solvents. EPR saturation factor and sample temperature under microwave irradiation could be obtained by measuring the relative NMR peak shift. Together with the determination of the leakage factor derived from proton T_1 measurements, the coupling factor, responsible for the DNP efficiency could be calculated and compared with TEMPOL.

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Host–Guest Complexes as Water-Soluble High-Performance DNP Polarizing Agents

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Dynamic nuclear polarization (DNP) enhances the sensitivity of solid-state NMR (SSNMR) spectroscopy by orders of magnitude and, therefore, opens possibilities for novel applications from biology to materials science. This multitude of opportunities implicates a need for high-performance polarizing agents, which integrate specific physical and chemical features tailored for various applications. Here, we demonstrate that for the biradical bTbK in complex with captisol (CAP), a β -cyclodextrin derivative, host–guest assembling offers a new and easily accessible approach for the development of new polarizing agents. In contrast to bTbK, the CAP-bTbK complex shows sufficient water-solubility for biological application and shows significantly improved DNP performance compared to the commonly used DNP agent TOTAPOL. On a large integral membrane protein reconstituted in lipid, the CAP-bTbK complex also outperforms TOTAPOL. The extrapolated DNP enhancement at infinite power of the new agent suggests that supramolecular assembling does not deteriorate the optimized geometry of the guest radical. G-band EPR measurements on concentrated radical solution at 100 K show that the electron longitudinal relaxation times (T_1) of this new agent are similar to those of TOTAPOL. The phase memory time (T_m) is longer than that of TOTAPOL in frozen solution. These data may explain the more efficient saturation of electron transition compared to TOTAPOL under the same microwave power in DNP experiments. Interestingly, while the new agent is used as paramagnetic dopant, matrix deuteration reduces ^1H T_1 by a factor of about 1.8, which yields an extra gain of NMR sensitivity per unit time. Meanwhile matrix deuteration of the matrix does not yield any significant changes on the electron T_1 in the biradical passing the whole EPR profile at high field. This is due to the locally concentrated proton cluster in the CAP-bTbK complex. A new strategy on breaking ^1H T_1 relaxation boundary in paramagnetic solids at low temperatures will be introduced accordingly. Besides the interesting findings on DNP performance as well as paramagnetic NMR features, we also observed that electron relaxation times in biradicals are highly orientation dependent at high field. This provides a new clue to the understanding of spin dynamics under DNP conditions. The numerous possibilities to functionalize host molecules will permit designing novel radical complexes targeting diverse applications.

Electron Spin-Spin Dipolar Interaction Role in High Field DNP Experiments on Liquid Radical Solutions

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Motion of radicals in liquid solutions plays an important role in Dynamic Nuclear Polarization (DNP) experiments especially in high magnetic field. The radical dynamics influences the Electron Paramagnetic Resonance (EPR) line shape as well as the coupling factor between the radicals and polarized nuclei. Recently, it was shown that the special features of this dynamics such as off-centered spin position in nitroxide and the collective dynamic effects (nitroxide clustering) can have a significant impact on DNP process [1]. In this work we access the characteristic parameters of the collective radical motion by observing the effects of the electron spin-spin dipolar interaction in CW EPR spectra [2]. This becomes possible at high radical concentrations (about 1 M) when the dipolar broadening dominates over the Heisenberg spin exchange. Taking the value of the diffusion coefficient of radicals in solution the distance of closest approach between the radicals can be detected. The CW-EPR experiments have been performed on TEMPOL radicals in different organic solvents at low (0.3 T) and high (9.2 T) magnetic fields. The evaluation of the experimental data provide a possibility to verify quantitatively the theoretically predicted characteristics of radical dynamic.

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Hyperpolarized ^{13}C NMR spectroscopy: a new way to follow the glutamate-glutamine cycle in-vivo

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Aim. Change in glutamate levels is involved in number of neurodegenerative diseases such as Parkinson's disease (Chassain et al, 2005; 2010). By the way to better understand the relationship between neurons and astrocytes, we use NMR spectroscopy and the highly amplified signal generated by hyperpolarization to achieve both spatial and temporal resolution adequate for in-vivo metabolism studies of the glutamate-glutamine cycle.

Methods. Experiments were performed on a 3T MR750 scanner (GEHC Milwaukee, USA), using a dual-tuned birdcage coil ($^1\text{H}/^{13}\text{C}$). Rats were anaesthetized with propofol. $[1-^{13}\text{C}]$ glutamate was hyperpolarized using Hypersense (Oxford Instruments). 30mM of hyperpolarized $[1-^{13}\text{C}]$ glutamate solution was administered via the carotid artery. To obtain an osmotic BBB disruption rats were previously infused with a hypertonic solution of 25% mannitol into the carotid. ^{13}C MRS was performed using a whole slice acquisition or a Spectral-Spatial (SPSP) excitation (Schulte et al, 2012). Data were acquired from a single transversal slice (20mm) through the brain with an acquisition each second. Data reconstruction was performed using MATLAB.

Results. $[1-^{13}\text{C}]$ glutamate was polarized by up to 15.8% in the liquid state and the T1 was 19.75s. Spectra acquired following injection of hyperpolarized glutamate showed the hyperpolarized ^{13}C -labeled carboxyl bolus and also the appearance of the signal of its metabolite the $[1-^{13}\text{C}]$ glutamine.

Conclusion. The hyperpolarized $[1-^{13}\text{C}]$ glutamate and its metabolite are imaged for the first time in-vivo inside the rat brain. Thus it may be a promising substrate for evaluation of glutamate-glutamine cycle activity in conjunction with neurodegenerative diseases.

Theory of Overhauser in Insulating Solids

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The Overhauser effect was the first prediction of the possibility to enhance nuclear polarization through microwave irradiation¹. Very soon after, it was experimentally demonstrated and nowadays, the Overhauser effect is routinely used in liquid state as well as in conducting solids²⁻⁵.

The mechanism presented by Overhauser requires the presence of a mobile electron. However an Overhauser effect in insulating solid has been predicted by Abragam⁶ in the case of a relatively high isotropic hyperfine coupling. Up to now, the phenomenon has been hardly observed and the first conclusive demonstration of Overhauser DNP at high field has been reported recently. In these experiments BPDA and SA-BDPA have been used as polarizing agents at high magnetic fields of 14 T and 18 T (equivalent to $\nu_n = 600$ and 800 MHz, proton larmor frequency) at 100 K and Magic Angle Spinning (MAS)⁷. Under such conditions, the DNP field sweep spectrum reveals the presence of a standard Solid Effect mechanism at $\pm\nu_n$ away from the EPR line as well as a positive enhancement at the center of the EPR line characteristic of an Overhauser effect, even though the samples are insulators.

To explain this observation of the Overhauser effect in an insulating solid we have developed a theoretical model simulating the MAS DNP process. In order to obtain the Overhauser effect we included two additional relaxation pathways through fluctuation of the hyperfine coupling, leading to Zero Quantum – ZQ ($\hat{S}^+\hat{I}^- + \hat{S}^-\hat{I}^+$) and Double Quantum – DQ ($\hat{S}^+\hat{I}^+ + \hat{S}^-\hat{I}^-$) relaxations. The observation of a positive enhancement can be explained by the existence of a faster ZQ relaxation mechanism with respect to the DQ.

Using this new method we have been able to explain most of the experimental features such as the power dependence as well as the field dependence. With this model we can also explain the differences between BDPA and SA-BDPA, and other radicals.

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Combining photo-CIDNP MAS NMR with strategies to determine structural dynamics in the photosynthetic process in natural reaction centers

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Magic-angle spinning (MAS) NMR is an established method for structural analysis as well as for elucidating local dynamics in solid materials, in particular polymers and proteins. Typical strategies for probing local dynamics involve measuring relaxation times, spin-diffusion experiments, Separated-Local-Field (SLF) NMR experiments etc [1]. The main interest of our work is to combine these strategies with the solid-state photo-CIDNP effect which allows for strong signal enhancement, and to investigate the function of the photosynthetic reaction centers (RCs) of *Rhodobacter sphaeroides* and of photosystem II of plants [2]. The photo-CIDNP effect has been detected in many natural photosynthetic RCs and it is believed to be a well preserved and inherent property of the photosynthesis process, and thus is expected to be directly related to the efficiency of the electron transfer [3,4]. By combining the signal enhancement originating from the photo-CIDNP effect, selectively site labeling and a Separated-Local-Field experiment, namely the DIPSHIFT experiment, that has been specifically designed for synthetic organic polymers, we expect to get insights into the structural dynamics occurring in the known static structures of the primary electron donors. Due to the selectively labeled sites, different kinetics trends can be predicted and suggestions for separate mobile and rigid components in the ¹³C spectrum, as well as extraction of residual coupling constants and order parameter of motion which hold information on the geometry and charge separation in the photosynthetic systems can be revealed [5].

Our aim is to investigate the role of structural dynamics in the photosynthetic process, namely during charge separation in reaction centers (RCs) of several natural photosynthetic systems. Reconstruction of the local molecular dynamics is expected to allow for better understanding of the selection of the electron transfer pathways in different photosystems.

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³He Spin Exchange Optical Pumping with ultra-narrow band laser

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A low - cost high - power laser diode array (LDA) can produce powers up to 100 W by integrating many individual laser diode emitters into a single array. The large spectral width, typically approximately 2-4 nm, of the LDA in comparison with 18 GHz/bar FWHM of Rb vapor absorption line strongly limits efficiency of SEOP process. Together with OPTIGRATE we design and build SEOP Laser which incorporates a unique volume Bragg grating design enabling ultra-narrow laser linewidth. The main characteristics of the laser system will be given together with results of systematic study of SEOP which clearly shows advantages of ultra-narrow band laser.

Proton spin noise from a hyperpolarized sample below 2K

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Nuclear spin noise spectra of hyperpolarized samples were previously observed in the liquid state on ¹²⁹Xe [1] (hyperpolarized by optical pumping) and on ¹H (after dissolution DNP) [2,3].

Here, first experimental data on proton spin noise (at 285.23 MHz) from solid samples below 2 K acquired on a home built DNP polarizer [4,5] ($v_{electron} \approx 188$ GHz) are presented. Varying the electron frequency allows variation of the nuclear polarization over large positive and negative values. Thus, one can test the Ernst/McCoy equation [6] over an unprecedentedly wide range. Depending on the electron frequency we have been able to observe both positive and negative spin noise line shapes, under conditions where pure spin noise [2] is not observable and radiation damping dominates.

The observation of spin noise allows monitoring hyperpolarization without interference by rf-irradiation.

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Level Anti-Crossings are a Key Factor for Understanding Magnetic Field Dependence of Hyperpolarization in SABRE Experiments

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A promising way of boosting low inherent sensitivity of NMR spectroscopy is given by the Signal Amplification by Reversible Exchange (SABRE) technique [1]. This is one of the few methods providing continuous production [2] of nuclear spin polarization, which exceeds thermal polarization by a factor of about 1000. Substrates get polarized in SABRE experiments without chemical modification: this is an advantage of SABRE in comparison with conventional Para-Hydrogen-Induced-Polarization method. However, despite the importance of the SABRE technique, until recently there was no quantitative assessment of polarization transfer from *para*-hydrogen to substrates at low magnetic field nor was the magnetic field dependence of SABRE understood.

We have found that polarization transfer in SABRE at low magnetic field occurs due to Level Anti Crossings (LACs) in scalar coupled multispin systems. The LAC concept allowed us to fully understand field dependences of SABRE at low magnetic fields. Specifically, we have established simple rules for signs of polarization of protons and determined the magnetic fields where polarization transfer is most efficient. Moreover, we investigated various substrates with two SABRE catalysts, Crabtree's catalyst [1] and IrMesCODCl [3], utilizing our recently build field-cycling. We have shown that scalar couplings of phosphorus (~20 Hz) with dihydride in case of Crabtree's catalyst significantly change the SABRE field dependence. Our measurements of the SABRE field dependences are in very good agreement with numerical calculation and simple analysis based on LACs in multispin systems [4]. The general concept of LACs used in our work allows one to explain complicated spin dynamic in multispin systems in SABRE experiment. We believe that LACs are a key factor, which determines spin dynamics in the SABRE technique.

The research was financially supported by the Russian Fund for Basic Research (projects No. 13-03-00437, 14-03-00397) and grant of the President of Russian Federation MD-3279.2014.2.

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Dedicated receiver array coil for ^1H lung imaging with same-breath acquisition of hyperpolarized ^3He and ^{129}Xe gas

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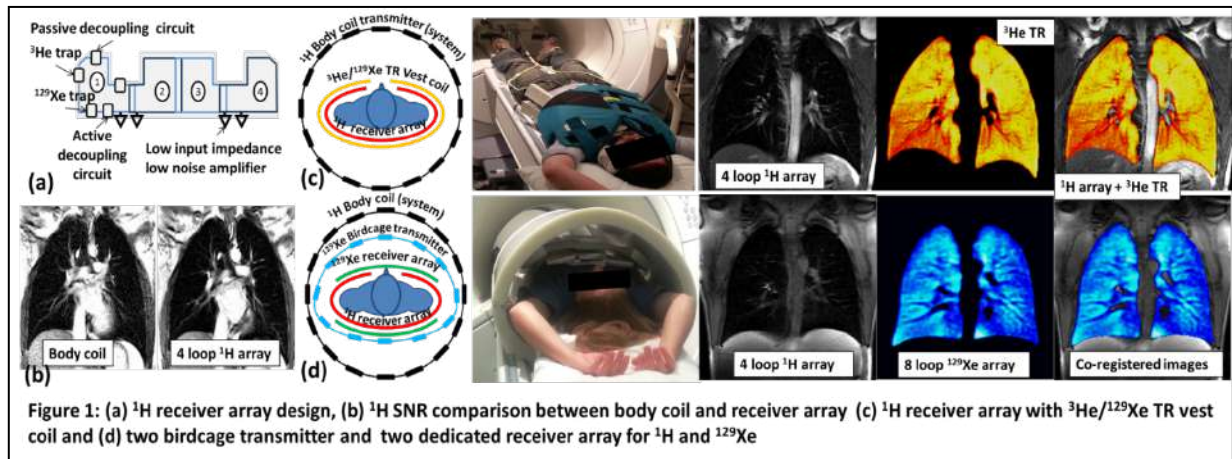
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Purpose: Same-breath acquisition of proton (^1H) and hyperpolarized (HP) gases in the lungs provide complementary structure-function information with inherent spatial-temporal registration^{3,4}. To date ^1H images have been acquired using the MR system's body coil, which has low SNR compared to dedicated receive only coils, this poses limitations when considering ^1H lung MR, as it is already a low SNR regime due to low tissue density and short T_2^* . The presence of TR coils at HP gas frequencies can further degrade the SNR obtained from the ^1H body coil. This study demonstrates the design and application of a dedicated ^1H surface array to improve the proton lung SNR in same-breath acquisition with HP gas ^3He and ^{129}Xe at 1.5T.

Methods: A 4 loop dedicated receiver array was developed in-house for ^1H lung MRI (63.83 MHz) to work in compatibility with a commercially available $^3\text{He}/^{129}\text{Xe}$ TR vest coil (CMRS, WI -without modifications) and an in-house ^{129}Xe asymmetric-birdcage transmitter¹ combined with ^{129}Xe receiver array as shown in Fig 1c&d. The resonant loops of the ^1H array were critically overlapped and it had a low input-impedance low noise amplifier ($\approx 2\Omega$). Loops were decoupled from the ^1H body coil transmit with one active and one passive detuning circuit. Each of the loops were fitted with passive traps for both ^3He (48.62 MHz) and ^{129}Xe (17.65 MHz). Lung MRI was performed on a GE 1.5T Signa HDx system with ^3He and ^{129}Xe gas polarized with spin exchange optical pumping². HP gas ventilation MRI and ^1H lung imaging were acquired back-back in the same breath. For ^3He ventilation MRI a spoiled gradient echo sequence was used with flip angle= 8° , TE=1.1ms, TR=3.6ms, matrix size = $104_{\text{phase}} \times 80_{\text{frequency}}$ slice thickness=10mm, FOV=38.4cm. For ^{129}Xe ; flip angle = 8° , TE =3.6ms, TR=18.9ms, matrix size = $78_{\text{phase}} \times 64_{\text{frequency}}$ slice thickness=15mm, FOV=38cm. For ^1H structural imaging a bSSFP sequence was used with flip angle= 50° , TE=0.9ms, TR=2.9ms, matrix size = $192_{\text{phase}} \times 256_{\text{frequency}}$. SNR was measured from *sum of squares* images as a ratio of mean of signal to standard deviation of noise.

Results: The SNR from the ^1H array was 2 folds more than the SNR from the ^1H body coil for same-breath acquisition with ^3He and ^{129}Xe TR coil in-situ (Fig 1b). The images from ^3He and ^{129}Xe were well co-registered with the images from ^1H (Fig 1c&d), consistent with their same-breath acquisition.

Discussion: Even though the ^1H array was tuned to 63.83MHz, which is well away from ^3He and ^{129}Xe frequencies, it was necessary to add traps to avoid coupling and protect the LNA. For the first case with the ^3He TR vest coil, ^3He traps were fitted to the ^1H array across a loop capacitor of 36pF. For the second case with ^{129}Xe TR vest coil, additional traps were added across another loop capacitor of 75pF. No reduction in ^1H or $^3\text{He}/^{129}\text{Xe}$ SNR was observed in both the cases. In the third case with two birdcage-transmitters/array-receivers for both ^1H and ^{129}Xe , the ^{129}Xe birdcage was not shielded to enable ^1H transmit.



Conclusion: The SNR improvement of the ^1H images provided by a nested ^1H receive array coil in the same-breath acquisition of HP gas MRI has been demonstrated. This is the first time ^1H array images have been acquired in same-breath acquisition with HP gas lung MRI and it is also the first time multi-nuclear imaging has been performed with two individual birdcage transmitters and two receiver arrays. Both represent novel developments in the field of multi nuclear MRI RF engineering and open up opportunities for the fusion of high quality images of structure (^1H lung MR) and function (HP gas MR) with obvious applications in other areas like ^{13}C metabolic imaging.

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Investigation of mechanisms of heterogeneous hydrogenation α,β -unsaturated carbonyl compounds by parahydrogen-induced polarization (PHIP)

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Parahydrogen-induced polarization (PHIP) is one of the most promising methods for increasing the sensitivity of NMR and MRI for several orders of magnitude. For PHIP observation the pairwise hydrogen addition is required, which means that reaction product or intermediate contains two atoms originating from the same parahydrogen molecule. As the result, the observation of PHIP effects indicates the existence of pairwise hydrogen addition route. Moreover, the significant enhancement of NMR signal produced by PHIP allows one to detect unstable intermediates and minor products. Therefore, PHIP technique can be successfully applied for the mechanistic studies of hydrogenation reactions as was demonstrated for the wide range of homogeneous and heterogeneous catalytic systems.

In this work PHIP technique was used for studying the mechanisms of heterogeneous hydrogenations of α,β -unsaturated carbonyl compounds. PHIP effects were observed in hydrogenation of C=C bond of acrolein and crotonaldehyde over different supported metal catalysts, demonstrating the existence of pairwise route of hydrogen addition to the substrate. In hydrogenation of acrolein over Pd-Sn/Al₂O₃, Pd-Sn/TiO₂, Pd-Zn/TiO₂ and Pd/TiO₂ catalysts with parahydrogen the proton of CHO group of propanal was also polarized. This can be explained by C(O)-H bond dissociation which represents a side process on the catalyst surface. Formation of polarized 2-butene was detected in hydrogenation of acrolein with parahydrogen over several Rh-based catalysts. This observation is made possible only due to the high NMR signal enhancement provided by PHIP. It was also found that hydrogenation of acetone and propanal with parahydrogen leads to polarized propane formation as a result of C-O bond hydrogenolysis.

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Rapid melt DNP

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A novel approach (Rapid-melt DNP) is presented to achieve fast proton spin hyperpolarization in small sample volumes. Rapid-melt DNP method combines efficient DNP in solid state with high resolution stripline NMR spectroscopy in liquid state. All common NMR experiments are compatible with this technique, including proton NMR, signal averaging, cross polarization and 2D spectra are possible. The sample is polarized at liquid nitrogen temperature using a high power EIK amplifier at 95 GHz. The NMR spectrum is acquired in liquid state on a stripline chip after rapidly melting the sample with warm nitrogen gas. A stripline chip provides optimal resolution and high sensitivity. We have successfully performed rapid-melt DNP on 50 nl sized sample volumes of both polar (aqueous) and nonpolar (toluene) solvents at 3.4 Tesla. DNP enhanced proton spectra of have been observed with enhancements 30-300, using both TEMPOL and BDPA radicals. For TEMPOL, we find typical evidence for Solid Effect DNP with a buildup time that is strongly reduced at high powers. Typical saturation is achieved at irradiation times below 20 seconds. Solid state Overhauser type enhancement have also been observed in these experiments when irradiation at the electron Larmor frequency. The same probe can also be used to examine Overhauser DNP in liquids and hyphenation with chromatography is possible. We will present some preliminary results, including DNP of a caffeine test sample containing 1 nanomole of molecules dissolved in 50 nl with good SNR at 3.4 T. The system can be easily be generalized for DNP at high magnetic fields if suitable mm-wave sources are available.

Uniting chromatography and NMR “on the strip”

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Our NMR group has for several years been optimising **stripline** inductors towards efficient NMR spectroscopy on small liquid sample volumes and mass-limited substances. Striplines are linear radiofrequency resonators that can yield much higher mass sensitivity than traditional “NMR coils” [1-3] **with detection limits currently 0.1 nanomole for liquid volumes between 100 nL – few μL .**

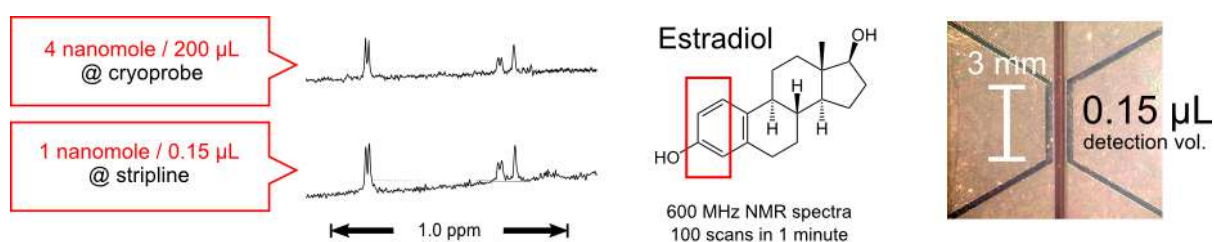


Figure 1. Sensitivity comparison at 600 MHz between a 3 mm length stripline NMR probe (150 nL detection volume) and a commercial 5 mm cryo-cooled NMR probe (200 μL detection volume).

This presentation demonstrates stripline NMR in hyphenation with the modern generation of **supercritical fluid carbon dioxide chromatography (SFC)** instrumentation for rapid and quantitative chemical analysis of mixtures. Key features of SFC are c. 5-10 times faster separations than high-performance liquid chromatography (HPLC), and that CO_2 contains no hydrogen atoms, thus avoiding background ^1H NMR signals. SFC minimises organic solvent use so is also considered on the “green” agenda.

I will demonstrate some on-line and off-line SFC-NMR hyphenations in characterising nanomole quantities of mixtures, and compare strategies for lowering the detection limit: **signal averaging; in-line concentration; and in-line nuclear spin hyperpolarisation using parahydrogen.**

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Towards Overhauser DNP in supercritical CO₂

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Liquid state Overhauser DNP is governed by electron-nuclear cross relaxations. At high magnetic fields these become less efficient if the translational correlation times are longer than the inverse Larmor frequency of the electron spin. In common liquids, the viscosity limits the diffusion dynamics and for large molecules the Overhauser DNP becomes rather small. In Supercritical solvents such as CO₂ under high pressures, the diffusion coefficient can be an order of magnitude larger and it is hypothesized that efficient liquid state DNP can persist up to high magnetic fields.

In this contribution we will present radical induced relaxation of methanol in supercritical CO₂ using in-line NMR coupled to a supercritical chromatography setup both at 144 and 600 MHz. These measurements can be used to estimate the concentration dependent cross relaxation. This can be used to model the cross relaxation and thus a prediction can be made for the possible DNP enhancement if full saturation of the EPR transition is realized. In this study solutions of 4-Hydroxy-TEMPO (TEMPOL) in methanol were injected into a capillary of supercritical CO₂ (sc CO₂). The resulting mixture was then measured using a stripline NMR probe.

Preliminary experiments at 95 GHz confirm the presence of Overhauser DNP even without a microwave cavity and for sample volumes that are an order of magnitude bigger than is common in aqueous solvents. This reflects the minimization of the dielectric heating in CO₂. We will discuss ongoing experiments to optimize the conditions for supercritical DNP.

Indirect Measurement of Absolute Spin Polarization via Scalar-Coupled Spy Nuclei in Dissolution Dynamic Nuclear Polarization

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Dissolution Dynamic Nuclear Polarization (D-DNP) has become a technique of choice for increasing the sensitivity of magnetic resonance up to 5 orders of magnitude [1]. By saturating the ESR transitions of polarizing agents such as TEMPOL at low temperatures and moderate magnetic fields (in our laboratory $T = 1.2$ K and $B_0 = 6.7$ T), the polarization of protons can be readily increased. The enhanced polarization can be transferred by cross-polarization from protons to nuclei of interest such as ^{13}C , ^{15}N , ^6Li , etc. One of the practical challenges of D-DNP is the determination of the nuclear spin polarization $P(^{13}\text{C})$, or equivalently the spin temperature $T_{\text{spin}}(^{13}\text{C})$ that can be achieved after dissolution and transfer to an NMR or MRI system. At room temperature, the hyperpolarized ^{13}C polarization $P_{\text{DNP}}(^{13}\text{C})$ is usually measured by comparing the signals observed immediately after dissolution with the thermal Boltzmann reference polarization $P_{\text{ref}}(^{13}\text{C})$ measured once the hyperpolarization has completely decayed, i.e., after waiting at least $10T_1(^{13}\text{C})$, so that the system has completely returned to thermal equilibrium. For concentrations in the mM range, 128 transients are typically needed to achieve a sufficient signal-to-noise ratio in thermal equilibrium, provided ^{13}C is isotopically enriched. Such measurements usually require more than 10 hours. They are virtually impossible in natural abundance. Thus the laborious observation of a reference ^{13}C signal to determine the thermal Boltzmann reference polarization $P_{\text{ref}}(^{13}\text{C})$ can actually require more time than the dissolution experiment itself.

We have investigated a simple method for the determination of the *absolute* polarization $P_{\text{DNP}}(^{13}\text{C})$ in hyperpolarized molecules in liquids which obviates the need for any time-consuming observation of the reference polarization $P_{\text{ref}}(^{13}\text{C})$ [2]. This can be achieved simply by measuring the *asymmetry* of multiplets in scalar-coupled pairs of spins immediately after dissolution. The method can be widely applied, provided that (i) that zero- and double-quantum cross-relaxation rates in the liquid state are significantly lower than the single quantum rates $1/T_1$ and $1/T_1$, and (ii) that cross-correlation rates due to interference of dipole-dipole (DD) and chemical shift anisotropy (CSA) interactions can be neglected [3].

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Optical Polarization of ^{13}C in Diamond via Nitrogen Vacancy Centers

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The nitrogen vacancy (NV) centre (Fig. 1) in diamond consists of a substantial nitrogen atom and a neighbouring vacancy [1]. This point defect is well investigated since the last decades and is recently one of the most prominent candidates for the realization of a quantum computer at room temperature and is for example already used as high sensitive magnetometer.

Furthermore their outstanding properties can help to overcome the Boltzmann population threshold in NMR experiments. The electronic structure of this defect enables an optical pumping in the spin ground state which makes a control of the spin via laser possible. With use of a magnetic field of about 50 mT one can create a level anticrossing (LAC) in the Zeeman splitting of the energetic substructures. This enforces a coupling to nearby spins, like the nitrogen or carbon-13 nuclear spins [2]. In recent studies an enhancement factor of about 500 at room temperature was observed [3]. To investigate this effect more in detail and optimize the polarization a whole new measurement setup is performed (Fig. 2).

In this contribution we will discuss the experimental concept and the first steps to the realization of our novel measurement design.

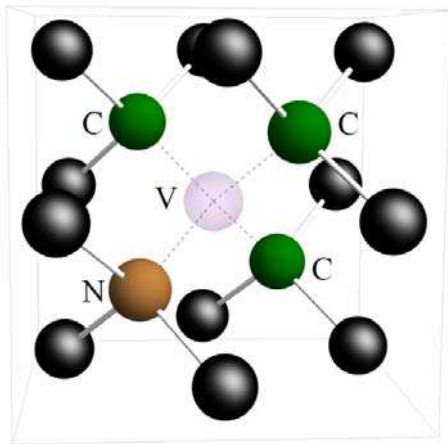


Fig. 1: Structure of the NV centre [1].

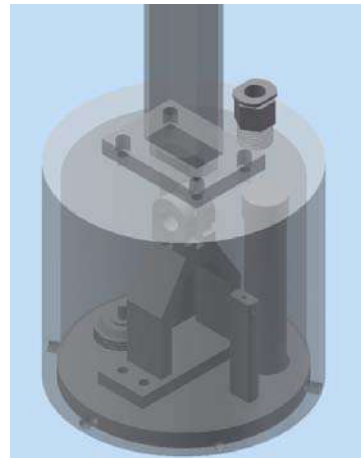


Fig. 2: Lower part of the NMR platform for fast sample transport into the superconducting solenoid.

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Dynamic nuclear polarization in the compensated semiconductor InP:Fe by optical pumping

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We present the optically pumped ^{31}P NMR in the compensated semiconductor InP:Fe. The creation of electron spins in a semiconductor by circularly polarized light, which can then drive dynamic nuclear polarization via the Overhauser or solid effects, is well known. Our NMR experiment was performed from 70 K to 140 K under 9.27 T. The population of the nuclear spins near the surface at 70 K is enhanced by ~ 34 , in comparison to the thermal equilibrium, by optical pumping. Our results show that 1) the NMR signal enhancement by optical pumping increases as the temperature decreases and 2) the phase of the NMR signal depends on the circular polarization of the light.

Nuclear hyperpolarization allows to explore fine structural tuning of fast electron transfer in short lived oxidized peptides

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The role of amino acid radicals as intermediates in electron and hydrogen transfer arouses growing interest in enzymology. The long-range electron-transfer (ET) reaction involving tyrosyl and tryptophanyl radicals is known to be of great importance in proteins. Time-resolved Chemically Induced Dynamic Nuclear Polarization (CIDNP) technique was applied to the investigation of reversible intramolecular electron transfer under acidic aqueous conditions in oxidized peptides of different structure containing tryptophan and tyrosine residues. Analysis of CIDNP kinetics allowed to obtain the rate constants of electron transfer in forward and reverse directions – from tyrosine residue to tryptophanyl cation radical, and from tryptophan residue to neutral tyrosyl radical. The influence of charge of terminal amino group, and the presence of glycine and proline spacers of the rate constants of the reaction under study has been established. The presence and the location of positive charge of the amino group has the greatest influence on the rate constant of IET to tryptophanyl radical cation, which varies by two orders of magnitude upon the change of order of linkage of residues into dipeptide: from $4 \times 10^3 \text{ s}^{-1}$ in oxidized Tyr-Trp to $5.5 \times 10^5 \text{ s}^{-1}$ in oxidized Trp-Tyr,¹ with rate constant for oxidized N-acetyl Trp-Tyr representing an intermediate case (Fig. 1). The rate constant of IET in reverse direction is less sensitive to the amino group charge.² The presence of glycine or proline spacers in the peptides with tryptophan residue at the N-terminus not only reduces the rate constants of IET, but also shifts the equilibrium towards the formation of tyrosyl radical compared to the peptide Trp-Tyr, meaning that the spacers affect the difference of reduction potentials of tryptophanyl and tyrosyl radicals.

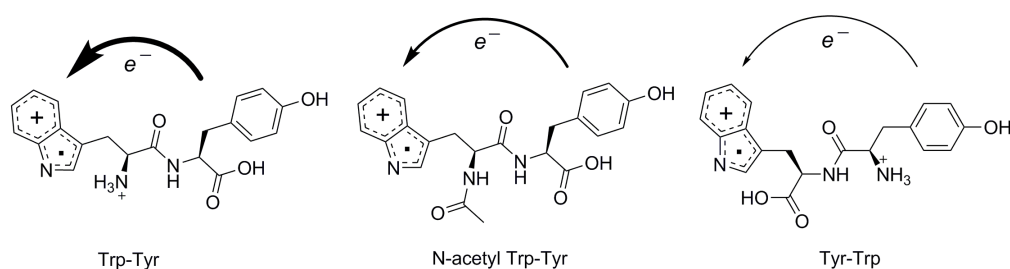


Fig. 1: Schematic illustration of the influence on the presence and location of terminal amino group charge on the efficiency of electron transfer from tyrosine to tryptophanyl radical cation in oxidized dipeptides.

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Towards functional analysis of photosynthetic reaction centers of diatom *Stephanopyxis turris* with photo-CIDNP MAS NMR

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Photo-CIDNP (photochemically induced dynamic nuclear polarization) is well-known from liquid state NMR where it has been observed for the first time in 1967. In 1994, Zysmilich and McDermott [1] demonstrated the solid-state photo-CIDNP effect in photosynthetic reaction centers (RCs) applying magic angle spinning NMR at low temperature to uniformly ¹⁵N-labeled, frozen and quinone blocked bacterial RCs of *Rhodobacter sphaeroides* R26.

The effect is caused by the strong electron polarization induced by continuous illumination with white light. From the initial radical pair, polarization is subsequently transferred to nuclei where it is detected by NMR as signal enhancement up to a factor of about 80,000. Two coherent mechanisms running in parallel, called “three spin mixing” and “differential decay”, transfer electron spin order to nuclear spin order [2]. In addition, due to a long triplet lifetime of the donor, a third mechanism, called “differential relaxation” occurs. The strong signal increase allows for observation of chlorophyll cofactors involved into photo-CIDNP in nanomolar concentration in intact cells [3].

In plants, e.g., the algae *Stephanopyxis turris*, two photosystems, PS I and PS II, are utilized, using sunlight to build up a proton gradient for ATP synthesis. Especially PS II shows unique capability in using electric potential to split even water: a process which is not fully understood. Photo-CIDNP MAS NMR [2] provides access to the heart of the photosynthetic RC and has been demonstrated on several RCs, e.g., those of *Rhodobacter sphaeroides*, spinach and duckweed. Here we aim for studying completely unknown reaction centers with this method which presently cannot be isolated from the algae.

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