



UNIVERSITÄT LEIPZIG

# **International Hyperpolarization Conference**

September 24-28, 2023 | Leipzig, Germany



# **Book of Abstracts**

https://www.hyp23.org

#### connections; seminar rooms with even numbers: VGA connections) \*On Tue 26 Sept, 12:15: Lunch Meeting of the AMPERE Subdivision Hyperpolarization: Seminar room S203. 17:20 18:00-21:00 17:00 15:15 14:30 13:45 13:00 (Entry Hall Augusteum) From 15:00 Registration 13:00-16:00 Tutorials (Chemistry building) Chair: E. Brunner Chair: M. Elgeti CIDNP (S. Cavagnero) (Entry Hall Augusteum) SEOP (E. Brunner) Welcome reception Dreydoppel (organ) Opening J. Matysik & M. (Hall Paulinum) NV centers (R. W. Warren (P) Wunderlich) Lab Tour 17:50 17:30 15:40 14:00 11:50 11:30 11:10 10:20 10:00 9:40 9:00 16:10 12:10 10:40 18:10 free evening Chair: B. Corzilius (Seminar rooms) Chair: G. Salvan Chair: S. Jannin Round tables I (Lecture hall 9) Mon 25 Sept. 5 round tables x 4x 20 5 round tables x 5x 20 J.P. Anserment (P) J. Kempf (Bruker) C. Tegenkamp Coffee Break D. Budker (I) A. Parker (I) Lunch break S. Glöggler V.V. Telkki B. Legrady Coffee J. Eills min min 15:40 14:00 11:50 11:10 10:20 10:00 9:40 11:30 10:40 9:00 12:10 Chair: M. Dvoyashkin (Seminar rooms) Chair: D. Budker Round tables II (Lecture hall 9) Tue 26 Sept. 5 round tables x 5x 20 City tours S. Björgvinsdóttir M. Lerche (P) Lunch break\* L. Chuchkova Coffee Break C. Bocquelet D. Kurzbach J. Wild (I) H. Heise Coffee min 19:00-23:00 17:30 14:00 9:40 9:00 16:10 15:40 12:10 11:50 11:30 11:10 10:40 10:20 10:00 Chair: F. Engelke Chair: M. Benatti (Seminar rooms) Chair: T. Gulder Round tables III (Lecture hall 9) Wed 27 Sept. 5 round tables x 4x 20 5 round tables x 5x 20 the Gondwana Land Conference Diner at T. Biedenbänder Coffee Break Y. Matsuki (I) T. Prisner (P P. Hore (P) Lunch break A. Capozzi W. Kilian O. Lafon O. Ouari Coffee (∠oo) min min 11:50 11:10 10:20 9:30 11:30 10:40 10:00 12:10 Chair: T. Prisner Chair: O. Lafon Thu 28 Sept. End of conference F. Mentik-Vigier (I) free S. Cavagnero (I) D.B. Bucher S. Jannin N. Yanai Goodbye Coffee

# HYP23 LEIPZIG 24-28 SEPT. 2023

Tutorials: Chemistry Building (Johannisallee 29, 04103 Leipzig): Large Lecture Hall (Großer Hörsaal). 5x Plenary talk (P, 40 min), 6x Invited talk (I, 30 min), 19x Promoted speakers (selected from Abstracts, 20 min): Lecture Hall 9 (City Center, at Augustusplatz) 115 slots (5x23) for round-table presentations: 5 min talk (power point), 12 min discussion, 3 min room change = 20 min slots (Seminar rooms with odd numbers: HDMI

# HYP23 LEIPZIG 24-28 SEPT. 2023 ROUND TABLE DISCUSSIONS

115 slots (5x23) for round-table presentations (within 5 lecture halls): 5 min talk (power point), 12 min discussion, 3 min room change = 20 min slots The most popular contributions will be presented twice.

	Mon 25 Sept.		Tue 26 Sept.		Wed 27 Sept.
	Round tables I		Round tables II		Rour
14:00	Table 1, Hall HS14, chair: Marina Benat	ti 14:00	Table 1, Hall HS14, chair: Sami Jannin	14:00	Table 1, Hall
14:00	Francesca Reineri RT 65	14:00	) Gaël De Paëpe RT 15	14:00	Dudari B. Buru
14:20	Koki Nishimura RT 52	14:20	) break	14:20	Rémi Blinder
14:40	Tomas Orlando RT 53	14:40	) Rubin Dasgupta RT 13	14:40	John Myers
15:00	Angeliki Giannoulis RT 22	15:00	) Deniz Sezer RT 76	15:00	Yunmi Kim
15:20	Nicolas Kempf RT 31	15:20	Deniz Sezer RT 76	15:20	Oleg G. Salniko
14:00	Table 2, Hall HS15, chair: Eike Brunne	14:00	Table 2, Hall HS15, chair: Olivier Lafon	14:00	Table 2, H
14:00	Mehdi Soussi-Therond RT 78	14:00	) Tobias Theiss RT 83	14:00	Yao Fu
14:20	Vladimir V. Zhivonitko RT 92	14:20	) Tomas Orlando RT 53	14:20	Friedemann Bu
14:40	Kristina Pilgaard Jacobsen RT 27	14:40	) Lauryas Dagys RT 12	14:40	Alexandra Nee
15:00	Obaid Mohiuddin RT 46	15:00	) Ertan Turhan RT 84	15:00	Ekaterina Pokc
15:20	Nele Reimets RT 64	15:20	) Igor V. Koptyug RT 36	15:20	Juha Vaara
14-00	Table 3 Hall HS16 chair: Dmitry Budke	14.00	Table 3 Hall HS16 chair: Olivier Ouari	14.00	Tahle 3 Ha
14:00	Nergiz Sahin Solmaz RT 70	14:00	) Johannes Bernarding RT 4	14:00	Patrick Hautle
14:20	Christopher Pötzl RT 59	14:20	) Daniel Cheney RT 10	14:20	Ditte Bentsen C
14:40	Thomas B. Wareham Mathiassen RT 87	14:40	) Henri de Maissin RT 14	14:40	Lorenzo Niccol
15:00	Michael Jurkutat RT 29	15:00	Wiebke Pohlandt RT 56	15:00	Pooja Pooja
15:20	Fatemeh Anvari Vind RT 2	15:20	)   Leif Schröder   RT 75	15:20	Vasvl Denvsen

16:10 16:30 16:50 17:10	16:10	16:10 16:30 16:50 17:10	16:10	16:10 16:30 16:50 17:10	16:10	
Andrei Kuzhelev RT 40 Yao Fu RT 20 Nathan Rougier RT 69 Takayuki Kumada RT 38	Table 5, Hall HS18, chair: Ville V. Telkki	Hiroyuki Yatabe RT 90 Nicholas Alaniva RT 1 Patrick Kurle-Tucholski RT 39 Katarzyna Dziubinska-Kuehn RT 18	Table 4, Hall HS17, chair: Wolfgang Kilian	Orit Nir-Arad Dominik Kubicki Oksana Bondar Vitaly Kozinenko RT 37	Table 3, Hall HS16, chair: Jim Wild	Mon 25 Sept.
						Tue 26 Sept.
16:10 16:30 16:50 17:10	16:10	16:10 16:30 16:50 17:10	16:10	16:10 16:30 16:50 17:10	16:10	
Lorenz Mitschang Philipp Groß Rémi Blinder Ronja Rößler	Table 5, Hall HS18, chair: Don	Francesca Reineri Milan Zachrdla Anika Mauel Andrei Kuzhelev	Table 4, Hall HS17, chair: Denni	Markus Plaumann Gian-Marco Camenisch Bulat Gizatullin Felix Schnabel	Table 3, Hall HS16, chair: Heni	Wed 27 Sept.
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#### WELCOME!

We are pleased to host the HYP23, the International Hyperpolarization Conference at Leipzig University from September 24-28, 2023!

The conference will provide a forum for fruitful scientific exchange, a valuable tool for competence building and knowledge transfer between the different methods of hyperpolarization. The program will consist of invited lectures and contributed papers. The conference language will be English.

As you may have recognized, we use the same logo that was designed for HYP21 in Lyon. Why? Because Leipzig is also a "lion city", because hyperpolarization is the "lion of magnetic resonance" and because we hope that future conferences will also use this beautiful logo, so that it becomes the logo for the entire series of conferences.

Leipzig University, found in 1409, is the 2<sup>nd</sup> oldest in the Federal Republic of Germany. People inspiring our field as Wilhelm Ostwald, Werner Heisenberg, Felix Bloch, Friedrich Hund, Peter Debye, Karl-Friedrich Bonhoeffer and Gustav Hertz have shaped the place. Arthur Lösche and Harry Pfeifer conducted in Leipzig the first NMR experiments on the European continent. Presently, the Magnetic Resonance Center (MRZ) links five faculties. Nobel Prize for Physiology or Medicine 2022 was received by the Leipzig researcher Svante Pääbo.

Cordially, Jörg Matysik, on behalf of the organizers

#### LOCAL ORGANIZING COMMITTEE

Marina Bennati, Göttingen Eike Brunner, Dresden Dmitry Budker, Mainz Björn Corzilius, Rostock Muslim Dvoyashkin, Leipzig Matthias Elgeti, Leipzig Frank Engelke, Großpösna Tanja Gulder, Leipzig Jörg Matysik, Leipzig Jan Meijer, Leipzig Georgeta Salvan, Chemnitz

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#### PRECEEDING HYPERPOLARIZATION MEETINGS

HYP21, Lyon, France, 2021 (Anne Lesage & Sami Jannin) HYP18, Southampton, England, 2018 (Malcolm Levitt & Giuseppe Pileio) Egmond aan Zee, The Netherlands, 2015 (Marc Baldus & Arno Kentgens)\* Zürich, Switzerland, 2014 (Matthias Ernst)\* Crete, Greece, 2013 (Bela Bode)\* Leiden, The Netherlands, 2012 (Brunner, Ivanov, Kentgens, Matysik) Novosibirsk, Russia, 2011 (Konstantin Ivanov & Hans-Martin Vieth) \*The three meetings from 2013 to 2015 were organized within the COST Action TD-1103.

#### PRECEEDING DNP MEETINGS

Copenhagen, Denmark, 2013 (Jan Henrik Ardenkjær Larsen) Lausanne, Switzerland, 2011 (Geoffrey Bodenhausen) Königstein, Germany, 2009 (Thomas Prisner) Nottingham, England, 2007 (Walter Köckenberger)

#### **OUR SPONSORS**

We cordially would like to thank our HYP23 sponsors:















# **PROGRAM OF THE TALKS**

# Sunday 24<sup>th</sup> September

17:20 Warren Warren Improving SABRE hyperpolarization using non-intuitive fields and sequences

# Monday 25<sup>th</sup> September

09:00 Jean-Philippe Ansermet *When spintronics and magnetic resonance cross paths* 

09:40 Christoph Tegenkamp *Electron spin polarization in polyalanine molecules in 2D and quasi-1D assemblies: the role of coupling, chirality and coordination* 

10:00 Bonifac Legrady Where does hyperpoarization go? Tracking of the evolution of a hyperpolarized spin system

10:50 Dmitry Budker *Hyperpolarization and zero- to ultralow-field (ZULF) NMR* 

11:10 James Eills *Parahydrogen-induced polarization for metabolic imaging in organ-on-a-chip devices* 

11:30 Ville-Veikko Telkki *Single-scan relaxation and diffusion methods for hyperpolarization applications* 

11:50 Stefan Glöggler Para-hydrogen enhanced magnetic resonance - new avenues to study hydrogenases and for in vivo applications

17:30 Anna Parker Hyperpolarized solution-state NMR spectroscopy via intermolecular NOE utilizing overwhelming source magnetization

17:50 James Kempf Solids DNP for 1.x GHz, SB magnets & HFX probes, plus dissolution DNP for the rest!

# **Tuesday 26th September**

09:00 Mathilde H. Lerche *Translation of dissolution DNP to the clinic: challenges and applications* 

09:40 Henrike Heise Protein folding observed at high sensitivity: Shedding light on chaotic systems

10:00 Charlotte Bocquelet *Performances of a tabletop flow DNP polarizer with porous matrices : towards recyclable hyperpolarization* 

11:10 Dennis Kurzbach Dissolution DNP access to material formation - Boosting resonances of short-lived intermediates above the detection threshold.

11:30 Snædís Björgvinsdóttir Development of a 28 T HTS gyrotron magnet for DNP

11:50 Liubov Chuchkova Dependence of photochemically induced dynamic nuclear polarization on wavelength, light intensity and magnetic field

# Wednesday 27th September

09:00 Thomas Prisner *New insides from liquid-state DNP performed at 9.4 T* 

09:40 Olivier Lafon *Observation of quadrupolar nuclei near surfaces using high-resolution MAS DNP and ultra-highfield NMR* 

10:00 Andrea Capozzi Across cities dDNP: strategies and challenges to make hyperpolarization transportable. 10:50 Yoh Matsuki Methods and instruments for high-field MAS DNP toward intracellular structural biology

11:10 Wolfgang Kilian *Routine Hyperpolarized 129Xe NMR utilizing a benchtop spectrometer* 

11:30 Olivier Ouari *Better biradicals for signal enhanced ssNMR DNP: a chemical affair* 

11:50 Thomas Biedenbänder A 2H approach towards investigation of methyl dynamics under DNP

17:30 Peter Hore *Radical pair magnetoreception: hyperpolarized birds?* 

# Thursday 28th September

09:30 Frederic Mentink-Vigier *PyrroTriPol and deuterated AsymPol from the viewpoint of simulations and experiments* 

10:00 Nobuhiro Yanai Triplet Dynamic Nuclear Polarization of Bio-relevant Molecules by New Polarizing Agents

10:50 Silvia Cavagnero *Marvels and challenges of LC-photo-CIDNP nuclear-spin hyperpolarization in liquids* 

11:10 Sami Jannin Dynamic nuclear polarization with polarizing matrices: from silica and epoxy to conductive polymers

11:30 Dominik B. Bucher *Microscale NV-NMR on a chip looking for hyperpolarization methods* 

# ABSTRACTS OF THE TALKS



#### IMPROVING SABRE HYPERPOLARIZATION USING NON-INTUITIVE FIELDS AND SEQUENCES

General theory, PHIP, Loss of hyperpolarization & relaxation

Warren Warren (1), Shannon Eriksson (1), Jacob Lindale (1), Xiaoqing Li (1), Mathew Mammen (1)

(1) Duke University, Durham, NC USA

SABRE operates in an unusual regime for magnetic resonance, where Zeeman splittings, scalar couplings, and exchange rates are all comparable. As a result, most of the assumptions that make NMR tractable are invalid. A practical consequence is that, while low fields offer the unique opportunity to fully manipulate fields in three dimensions, very little exploration of parameter space has been done. This is important because current advantages of SABRE (low cost, rapid polarization, broad ligand suitability) are counterbalanced by generally lower polarization levels than d-DNP.

This presentation will develop a comprehensive picture of SABRE evolution dynamics, generated by the recent development of rapid simulation tools[1] and validated by experiment. For example, sequences of rectangular or shaped z-fields which never approach a matching condition can improve polarization. [2,3] We also report two approaches with multiaxial pulse sequences that facilitate direct measurement of the initial coherent dynamics in this complex system, and improve magnetization yields up to 7-fold and singlet yields up to 4-fold. The first approach, analogous to many high-field experiments, used decoupling along a perpendicular axis to preserve hydride singlet order. The second approach gets away from assuming a sequence structure, and used an evolutionary strategy to optimize polarization under an arbitrary multiaxial field. The field generated by this Multi-Axis Computer-aided HEteronucular Transfer Enhancement approach (MACHETE SABRE) improves polarization more than 7-fold over continuous field SABRE SHEATH. An average Hamiltonian approach turns out to be insightful to understand this. These waveforms, compatible with any 3-channel AWG and a simple multiaxial coil array, present a new strategy for understanding polarization transfer and optimizing population transfer in both magnetized and singlet states.

#### Literature:

[1] J. Lindale, S. L. Erkisson, S.P.N. Tanner and W. S. Warren, Science Advances 6, abb6874 (2020)[2] S. L. Eriksson, J. R. Lindale, X. Li and W. S. Warren, W. S. Science Advances 8, abl3708 (2022)[3] X. Li, J. R. Lindale, S. L. Eriksson, and W. S. Warren, Phys. Chem. Chem. Phys. 24 16462-16470 (2022).[4] S. L. Eriksson, M. W. Mammen, C. W. Eriksson, J. R. Lindale and W. S. Warren, JMR 342, 107282 (2022).

#### Jean-Philippe Ansermet jean-philippe.ansermet@epfl.ch



#### WHEN SPINTRONICS AND MAGNETIC RESONANCE CROSS PATHS

Jean-Philippe Ansermet (1)

(1) École Polytechnique Fédérale de Lausanne, Switzerland



Invited to talk about research at the intersection of spintronics and magnetic resonance, I will start my survey with magnetoresistive detection of magnetic resonance, from Juretschke's time to the days of the "spin diode" effect. After a quick reminder concerning spin accumulation – a hallmark of GMR – I will allude to the natural enhancement of NMR in ferromagnet and present unpublished results on the detection of spin accumulation by NMR. I will claim that transmission electron spin resonance is an ancestor to spintronics devices and point to the giant ESR enhancement obtained in this type of spectroscopy. After defining spin pumping, I will show how magnetic resonance can detected by the inverse spin Hall effect and point to an experiment showing zero-field electron spin polarization obtained by driving a current through a non-symmorphic crystal. I will report on our demonstration of chirality-induced spin selectivity observed in the charge transfer rate at functionalized electrodes in an electrochemical environment. This work led us to try and succeed in achieving electrochemical dynamic polarization. The talk concludes with our demonstration of cavity-mediated resonances in anitferromagnets.



#### ELECTRON SPIN POLARIZATION IN POLYALANINE MOLECULES IN 2D AND QUASI-1D ASSEMBLIES: THE ROLE OF COUPLING, CHIRALITY AND COORDINATION

Thi Ngoc Ha Nguyen (1), Lech Thomas Baczewski (2), Yossi Paltiel (3), Georgeta Salvan (1), Olav Hellwig (1), Christoph Tegenkamp (1)

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 (3) Department of Applied Physics, Hebrew University of Jerusalem, Jerusalem 91905, Israel

Propagation of electrons along helical polyalanine-based backbone structures comes along with a robust spin hyperpolarization effect. However, studies on a molecular scale are still rare, although this length scale provides direct insight into the role of molecular properties.

In a first step, we analyzed by scanning tunneling microscopy (STM) the adsorption process of ????-helix polyalanine (PA) molecules of different lengths (up to 5.4nm), helicities (L, D), sequences (alanine helix w/ and w/o lysine) and different terminations (w/ and w/o cysteine) from solution on various surfaces. Enantiopure solutions result in formation of densely-packed films of upright-standing molecules. The high packing density is a result of interdigitation and comes along with a well-ordered molecular film [1, 2]. For mixtures of L- and D-PA, heterochiral dimers with a rectangular unit cell for DL-PA are formed. Despite the steric hindrance, the packing density of the DL-PA heterophase is increased compared to the enantiopure phase [3].

In order to study the spin polarization along the PA molecules, the different molecular phases were realized on magnetically switchable Al2O3/Pt/Au/Co/Au substrates and the electron transmission was probed by scanning tunneling spectroscopy (STS). Thereby, a correlation between the PA molecules ordering at the surface with the electron tunneling across this hybrid structure as a function of the substrate magnetization orientation as well as the coverage density and helicity of the PA molecules was found [4]. The spin polarization reaches up to 70% for chemisorbed molecules arranged in a hexagonal phase and is considerably lowered for the heterophase, shorter PA molecules and PA molecules without a cysteine termination [5]. Our results clearly demonstrate that both the coupling to the substrate as well as the ordering and coordination are important in order to understand microscopically hyperpolarization in such chiral systems.

[1] T.N.H. Nguyen, D. Solonenko, O. Selyshchev, P. Vogt, D.R.T. Zahn, S. Yochelis, Y. Paltiel, C. Tegenkamp, J. Phys. Chem. C, 2019, 123, 612.

[2] T.N.H. Nguyen, D. Sharma, D. Slawig, S. Yochelis, Y. Paltiel, D.R.T. Zahn, G. Salvan, C. Tegenkamp,

J. Phys. Chem. C, 2020,124, 5734.

[3] T.N.H. Nguyen, S. Xue, C. Tegenkamp, J. Phys. Chem. C, 2020, 124, 11075.

[4] T.N.H. Nguyen, L. Rasabathina, O. Hellwig, A. Sharma, G. Salvan, S. Yochelis, Y. Paltiel, L.T. Baczewski, C. Tegenkamp, ACS App. Mat.& Int., 2022, 14, 38013.

[5] T.N.H. Nguyen, Y. Paltiel, L.T. Baczewski, C. Tegenkamp, ACS Appl. Mat. & Int., 2023, 15, 17406.

#### M. Bonifac Legrady m.b.legrady@soton.ac.uk



#### WHERE DOES HYPERPOLARISATION GO? TRACKING THE EVOLUTION OF A HYPERPOLARISED SPIN SYSTEM

M. Bonifac Legrady (1), Mohamed Sabba (1), Quentin Chappuis (2), Stuart J. Elliott (3), Sami Jannin (2), Malcolm H. Levitt (1)

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 (2) Université de Lyon, CNRS, Université Claude Bernard Lyon 1, F-69100 Villeurbanne, France
 (3) Molecular Sciences Research Hub, Imperial College London, London, W12 0BZ, UK

Hyperpolarisation techniques can provide very large spin polarisation and huge NMR signal enhancements. Most of us have seen this statement in some form countless times, but what does it actually mean? Why is that? Is hyperpolarisation signal enhancement then? What kind of polarisation do we generate? Where does it go? These questions are relatively straightforward to answer for isolated spins. This is far less easy for coupled multi-spin systems. In this work we investigate this issue using dissolution DNP (d-DNP) experiments on a strongly coupled <sup>13</sup>C two-spin system. To address this, one needs to determine the precise state of the spin-system, which is possible even from the simplest experiments via careful analysis of the data. A straightforward analysis method will be presented that allows quantification of all reasonably possible spin states immediately after dissolution, and after two different preparation sequences. In the present system, a single spectrum contains sufficient information, and thus, the evolution of the entire density operator can be followed until signal can be detected. This technique may be applied to any multi-spin system, when resonances are well resolved and precise peak intensities can be obtained, to extract maximal information about the density operator. It is clearly demonstrated that in a strongly coupled spin-pair system, a significant amount of singlet order is generated directly by d-DNP. This is a long-lived spin order, which, in this system, has a relaxation time of approximately 60 seconds, which is 26 times longer than the value of T<sub>1</sub>. It is shown experimentally that after dissolution, the three triplet states rapidly reach an internal equilibrium, while the singlet population persists in a non-equilibrium state for a long time. Some further singletassisted d-DNP experiments will be proposed and illustrated by spin dynamical simulations.



#### HYPERPOLARIZATION AND ZERO- TO ULTRALOW-FIELD (ZULF) NMR

PHIP, Optical pumping & SEOP, CIDNP and ONP (incl NV centers), Triplet DNP, Loss of hyperpolarization & relaxation

Dmitry Budker (1)



(1) Johannes-Gutenberg-Universität Mainz

Hyperpolarization is a necessity, rather than a luxury, for zero- to ultralow-field (ZULF) NMR. In fact, ZULF NMR has been developing hand-in-hand with the developments in hyperpolarization. We will give examples of ZULF NMR work, together with our numerous collaborators, with pre-polarization in a strong magnet followed by sample shuttling, parahydrogen induced polarization (including SABRE), dissolution dynamic nuclear polarization, photochemically induced polarization (photo-CIDNP), and perhaps nuclear polarization in/with diamond.

Τ5

#### James Eills jeills@ibecbarcelona.eu



#### PARAHYDROGEN-INDUCED POLARIZATION FOR METABOLIC IMAGING IN ORGAN-ON-A-CHIP DEVICES

General theory, General Instrumentation, Applications, PHIP

James Eills (1), Marc Azagra (1), David Gomez Cabeza (1), Alba Herrero Gomez (1), Irene Marco Rius (1)

(1) Institute for Bioengineering of Barcelona

Organ-on-a-chip (OoC) platforms are microfluidic devices in which cells can be cultured in a 3D environment to replicate the structure and function of human organs.[1] These microfluidic devices allow experiments to be carried out with a high degree of repeatability and experimental control, and provide a route to personalized medicine and to replace animal testing. Many diseases affect cellular metabolism (e.g., cancers), and the changes in metabolic flux provide a marker to track the disease progression and response to treatment. In this work we are developing a multi-sample OoC platform to study the metabolic activity of cell-laden 3D structures. We aim to parallelize experiments by culturing multiple samples on one device, using magnetic resonance spectroscopic imaging (MRSI) as a noninvasive method to track metabolic flux with sufficient spatial resolution to distinguish each sample.[2]

In our lab we are using PHIP to hyperpolarize the metabolite [1-13C]fumarate, which is a marker for cell necrosis.[3] This involves chemically reacting a precursor molecule with parahydrogen gas to yield a hyperpolarized product, and then purifying it from the reaction solution, ready for perfusion into organoids in OoC devices. PHIP carries significant advantages for coupling with OoC microfluidics: both methods are low-cost and yield a high experiment turnover rate. Using PHIP, it is possible to produce hyperpolarized solutions with a turnover rate of mere minutes, offering the possibility for pseudo-continuous metabolic monitoring.

In recent experiments, we have hyperpolarized [1-13C]fumarate via PHIP, and injected the sample into a four-well microfluidic platform. After the sample filled the four wells, we performed 16x32 voxel 13C chemical shift imaging and were able to spatially distinguish the four samples. We are now preparing to repeat these experiments with an immortalized hepatocyte mouse cell lines (AML12),[4] with the aim of observing fumarate->malate conversion as a marker for cell necrosis.

[1] C. M. Leung, P. de Haan, K. Ronaldson-Bouchard et al., A guide to the organ-on-a-chip, Nat. Rev. Methods Primers 2022, 2, 33

[2] M. Azagra et al. Proc. Int. Soc. Magn. Res. 852 (2023)

[3] M. Gierse, L. Nagel, M. Keim, et al., Parahydrogen-polarized fumarate for preclinical in vivo metabolic magnetic resonance imaging, J. Am. Chem. Soc. 2022

[4] A. Herrero, M. Azagra, I. Marco-Rius, Biomed. Mater. 21, 17(4), 2022



#### SINGLE-SCAN RELAXATION AND DIFFUSION METHODS FOR HYPERPOLARIZATION APPLICATIONS

Ville-Veikko Telkki (1)

(1) NMR Research Unit, University of Oulu, Finland



# Spatial encoding allows single-scan multidimensional relaxation and diffusion experiments and facilitate the use of hyperpolarization to boost sensitivity.

Many standard relaxation and diffusion experiments, such as inversion recovery and PGSE experiments, need to be repeated several times with an incremented time delay or gradient strength to determine a single relaxation or diffusion parameter. Furthermore, standard multidimensional experiments require always multiple repetitions to collect the data of indirect dimensions. The need for repetitions makes the use of hyperpolarized substances more difficult, as the hyperpolarized state should be reproduced before each repetition, hyperpolarization process is often very time consuming, and the obtained hyperpolarization level may vary.

Based on the principles of spatial encoding [1], in which the data of indirect dimension are encoded into layers of a sample, we have developed a set of single-scan relaxation and diffusion experiments [2]. Some of the experiments, such as ultrafast T1-T2 and D-T2 experiments [3,4], allow correlation between different relaxation and diffusion parameters, while some others, such as ultrafast DEXSY and REXSY, enable to study molecular exchange phenomena via relaxation and diffusion contrast [5,6]. Recently, we introduced also a single-scan T1rho experiment [7].

The single-scan experiments significantly facilitate the use of nuclear spin hyperpolarization to enhance sensitivity of experiments. We have demonstrated the feasibility of the ultrafast relaxation and diffusion experiments with dDNP [4,6], PHIP [4], SABRE [8] and SEOP hyperpolarization methods [9]. We have also shown that the hyperpolarized single-scan multidimensional relaxation and diffusion experiments are feasible even with portable, single-sided, low-

field NMR instruments [10-12]. The applications range from studies of aggregation of surfactant solutions [5] to identification of intra- and extracellular metabolites in cancer cells [6].

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- [2] V. V. Telkki et al. Prog. Nucl. Magn. Reson. Spectrosc. 126-127 (2021) 101-120.
- [3] S. Ahola, V.-V. Telkki, ChemPhysChem 15 (2014) 1687-1692.
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- [6] G. Zhang et al. Anal. Chem. 90 (2018) 11131-11137.
- [7] K. Tolkkinen et al. Phys. Chem. Chem. Phys, 25 (2023) 13164.
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- [9] O. Mankinen et al. Microporous Mesoporous Mater. 269 (2018) 75-78.
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- [11] Y. Kharbanda et al. Angew. Chem. Int. Ed. 61 (2022) e202203957.



#### PARA-HYDROGEN ENHANCED MAGNETIC RESONANCE - NEW AVENUES TO STUDY HYDROGENASES AND FOR IN VIVO APPLICATIONS

Stefan Glöggler (1)

(1) Max Planck Institute for Multidisciplinary Sciences

Para-Hydrogen Induced Hyperpolarization is an emerging field of research which started in the late 80s and 90s with an emphasis on studying catalysts and metal complexes [1,2]. In recent years para-hydrogen hyperpolarization techniques have advanced to a stage were metabolic in vivo studies have become possible [3-5].

I would like to present the most recent developments of my lab using para-hydrogen.

This will include on one side our most recent studies on using para-hydrogen enhanced pyruvate in vivo to differentiate various forms of cancer and new approaches to study brain and liver. On the other side I will show our successfull implentations of para-hydrogen to study hydrogenases. Hydrogenases are an important class of enzymes that is found in some microorganisms and serves in the hydrogen activation process that these organisms require for energy production. These enzymes are considered nature's blueprint for effective catalysts involving hydrogen. Our para-hydrogen studies allowed us to reveal steps of the catalytic cycle that no other technique could probe and therefore largely adds to the understanding of this important class of enzymes [6].

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#### HYPERPOLARIZED SOLUTION-STATE NMR SPECTROSCOPY VIA INTERMOLECULAR NOE UTILIZING OVERWHELMING SOURCE MAGNETIZATION

Liquid DNP

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#### Background-subtracted, HYPNOESYS-hyperpolarized spectrum of a mixture of small solvent molecules.

Nuclear spin hyperpolarization provides a promising route for increasing sensitivity in NMR research and applications. One technique in this body of methods involves hyperpolarizing target nuclei in solution by cross-relaxation from another source molecule/atom via intermolecular NOE [1]. Recently, we demonstrated that this format of hyperpolarization can produce significant enhancements when using 1H source nuclei in highly polarized and highly concentrated solutions. In a first implementation, we demonstrated this with the 1H nuclear spins in naphthalene by dissolving optically-polarized pentacene-doped naphthalene crystals into organic solutions [2]. Using this method, which we called the Hyperpolarized NOE System (HYPNOESYS), we observe enhancements up to 2600 (60 MHz), 50 (400 MHz), and 40 (600 MHz) for 1H on molecules up to 290 Da. Furthermore, we demonstrate that this technique can be coupled with ultrafast methodology employing spatial parallelization to acquire hyperpolarized 2D 1H-1H correlation spectra of a mixture of terpene molecules in a single scan.

In order to make this method better suited to high-throughput experiments, we have adapted the technique to utilize a parahydrogen-polarized source molecule instead of optically-polarized naphthalene. Our technique bypasses the specificity typical of PHIP-based methods and allows broad applications to target molecules by separating the process into two steps. First, the hydrogenation and polarization process is tailored to one specific intermediate source, and then transfer to target molecules is enabled via intermolecular NOE. We chose (1-13C,d6)-dimethyl maleate as a first intermediate source which is produced in seconds by reacting (1-13C,d6)-dimethyl acetylenedicarboxylate with parahydrogen in acetone-d6. Parahydrogen-derived singlet order is then converted to 1H magnetization using low-field polarization transfer protocols similar to those developed for highfield NMR [3]. In a final step, the solution of (1-13C,d6)-dimethyl maleate is mixed with target molecules to enable polarization transfer.

Our current work is focused on improving the quality of the hyperpolarized spectra through source suppression, hyphenating our method with ultrafast two-dimensional spectroscopy, and initial testing of various possible applications. We will discuss recent advances in these efforts using both optically-polarized and parahydrogen-polarized intermediate source molecules.

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#### TRANSLATION OF DISSOLUTION DNP TO THE CLINIC: CHALLENGES AND APPLICATIONS

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20 years ago the first papers were published showing that small molecules hyperpolarized with solid state DNP can be brought into solution without signal loss and used as imaging agents. Since then several research fields have emerged and the vision of being able to apply measurements of cellular function for clinical diagnosis and treatment with magnetic resonance seems no longer far-fetched.

During this talk we will be looking at the technical boundaries for the use of dDNP in clinical applications. Including biological and physical demands on imaging agents, dDNP instrumentation, multinuclear MR acquisition hardware and pulse sequences. Also, highlights will be given on the advances in using dDNP MR to study cellular function for clinical applications.

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#### Henrike Heise



# PROTEIN FOLDING OBSERVED AT HIGH SENSITIVITY: SHEDDING LIGHT ON CHAOTIC SYSTEMS

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random coil chemical shifts in a disordered protein (left) reflect an average of different secondary shifts sampled during the experiment, and which all become visible in frozen solution (right)

NMR-spectra obtained at cryogenic temperatures below 150 K usually suffer from severe inhomogeneous line broadening, as flexible parts of molecules may be trapped in different conformations with different chemical shifts. While broad lines result in limited resolution and thus are considered an unwanted side-effect of low temperatures, they encode valuable information about conformational distributions of the backbone as well as of side chains. A combination of dedicated isotope labeling techniques with DNP-enhanced MAS-NMR-spectroscopy of proteins in frozen solution can shed light onto different conformational ensembles sampled by protein backbone as well as by amino acid side chains [1-4].

We exploited DNP-enhanced MAS NMR spectroscopy at low temperatures (~100K) to investigate conformational ensembles of proteins at different stages of protein folding and with different degree of order, respectively. We studied the distribution of backbone conformations in the intrinsically disordered protein  $\alpha$ -synuclein in frozen solution in different surroundings by evaluating the inhomogeneously broadened line-shapes one C $\alpha$ /C $\beta$  cross peak [2,3]. We could estimate the amount of disordered regions in fibrillar  $\alpha$ -syn and delineate the membrane binding regions of  $\alpha$ -syn in contact with membrane surfaces in in different protein to lipid ratios. We also found that secondary chemical shifts of neighboring amino acids tend to be correlated, a finding which suggests the formation of transient secondary structure elements.

Next, we investigated conformational sampling of the side chains of the amino acid isoleucine in different proteins

at different stages of protein folding.

Chemical shifts of side-chain carbon atoms reflect the side-chain torsion angles  $\chi 1$  and  $\chi 2$  [4]. We studied the conformational space sampled by isoleucine side chains in different conditions: in a peptide with random coil conformation, in globular proteins like GABARAP, the well-folded protein PI3K-SH3, which is prone to unfolding at low pH, as well as in intrinsically disordered proteins (IDPs) like  $\alpha$ -synuclein. The spectral differences between isoleucine in a well-ordered system in comparison to an IDP, provide valuable information about conformational freedom in different protein regions in general and yield important insights into protein folding and unfolding.

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Dissolution/Melt DNP

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Hyperpolarization methods provide a way to tackle the inherently low NMR sensitivity and acquire a higher signal intensity in a shorter time. Twenty years ago, dissolution Dynamic Nuclear Polarization (d-DNP) [1] was introduced and is now one of the hyperpolarization methods providing boosts of more than 10'000-fold in sensitivity on a routine basis.

However, this method suffers from two drawbacks narrowing its use. The overall hyperpolarization experiment is i) destructive and ii) single shot. Indeed, the frozen sample, once polarized, is dissolved before being analyzed in liquid state NMR. During this process, it is inevitably diluted, and its signal vanishes within seconds, therefore it cannot be repolarized. On the other hand, the most valuable NMR experiments rely on repeated acquisition, including incremented time steps for multidimensional acquisition and phase or gradient modulation for coherence selection and error correction. In d-DNP, this is not possible due to the single-shot nature of the experiment.

We are presently working on turning d-DNP into a new version widely compatible with NMR spectroscopy. It consists in replenishing the DNP hyperpolarization of a sample flowing through a closed loop, without dilution nor contamination using hyperpolarizing silica-based material (HYPSO) as polarizing matrices [2,3] in a compact and helium-free DNP polarizer coupled to a benchtop NMR spectrometer for liquid-state detection.

Here, I will briefly present the design and performances of the DNP polarizer, and elaborate on the DNP enhancements, on both 1H and 13C, using water-soluble radicals in frozen solutions and impregnated HYPSO matrices. Indeed, HYPSOs can be easily filtered to produce pure hyperpolarization that will ultimately be replenished. Finally, I will present preliminary results regarding the flow setup.

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We acknowledge Bruker Biospin for providing the prototype benchtop DNP polarizer and particularly D. Banks, R. Melzi, and J. Kempf for scientific and technical support. This research was supported by ENS-Lyon, the French CNRS, Lyon 1 University, the Institute of Chemistry at Lyon (ICL), the European Research Council under the European Union research and innovation program (ERC Grant Agreements No. 101044726 / HypFlow) and the French National Research Agency (project 'HyMag' ANR-18-CE09-0013).

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#### DISSOLUTION DNP ACCESS TO MATERIAL FORMATION - BOOSTING RESONANCES OF SHORT-LIVED INTERMEDIATES ABOVE THE DETECTION THRESHOLD.

General Instrumentation, Applications, Dissolution/Melt DNP

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#### Recent advances of Dissolution DNP enables access to complex material formation events.

The capacity to rationally design functional materials is a critical societal objective whose relevance is currently dramatically exposed by the pressing need for materials tailored for tasks from energy storage to vaccine delivery to superior CO2 filters.

Today, still, the most advanced materials are those found in nature. These evolutionarily optimized substances provide exceptional efficiencies, e.g., in harvesting solar energy (diatoms) or extreme endurance (bone), are intrinsically biocompatible, and offer a highly desirable ecological fingerprint – particularly considering the global waste problem and recent climate predictions. Gaining control over the pathways leading to these materials to enable engineering of next-generation functional materials lies is a core prerequisite to enable design of next generation biomimetic materials.

Strikingly, despite intense and international research efforts, mimicry of biological materials is still limited to only

a few successful applications. True exploitation of this immense potential remains unreached since the tools allowing one to recreate natural biominerals are still lacking. This prevailing shortcoming is due to a lack of insight into the molecular mechanisms at work. Only recently, it was evidenced that biomaterials do not form via the established nucleation-and-growth mechanism often observed in in-vitro settings. Instead, a material's function, shape, and morphology are predetermined by supramolecular precursors, so-called prenucleation species (PNS)[1], that self-assemble in solution from combinations of peptides and inorganic salts. These assemblies act as early-stage solution-state templates for solid biomaterials and precipitate from solution only upon external stimulation – a natural process to produce vital materials on demand.

These templates' structural dynamics remain unknown, impeding truly rational biomimetic design. Most critically, due to their high molecular weights and complex dynamics, PNS evade characterization by the only available tool for high-resolution solution-state structure determination, namely, NMR spectroscopy.

In this contribution, we demonstrate that hyperpolarization by dissolution dynamic nuclear polarization can help overcome this predicament by enhancing the resonances of PNS, thus, enable tracing their activity during material formation. From the solution-state self-assembly to the precipitation of a functional solid, the recent developments in DDNP methodology (incl. novel, rapid injection systems, alternative radicals, multiplexed detection of cross-relaxation paths) allow for these challengin observations.

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#### DEVELOPMENT OF A 28 T HTS GYROTRON MAGNET FOR DNP

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MAS DNP has been moving towards higher magnetic fields over the last decades, but one of the associated challenges is that the efficiency of the most commonly use continuous wave polarization transfer mechanisms scales inversely with increase in magnetic field. Time-domain DNP is considered a promising alternative to continuous wave DNP at high fields, with the main technical challenge being the generation of high-power and high-frequency microwaves.[1] We suggest that time-domain DNP at 28 T may be achieved with a frequency-agile fundamental cyclotron harmonic gyrotron, designed to generate kilowatt-level power of microwaves at a frequency of 792 GHz, with the option of fast frequency tuning over a range of at least 1 GHz. This gyrotron, which is currently under design, requires a magnet with a field similar to that of the NMR magnet.

Here, we present our progress towards building a 28 T gyrotron magnet out of high-temperature superconducting (HTS) tape. This superconductor consists of rare earth barium copper oxide (REBCO) ceramics, which has a higher critical magnetic field than conventional low-temperature superconductors, allowing it to generate very high magnetic fields. [2] The high current density of HTS also makes the magnets compact, which can provide additional flexibility in the gyrotron design. Gyrotron magnets do not have the same stringent requirements as NMR magnets when it comes to field homogeneity and stability, and can be operated in non-persistent mode. The 28 T all-HTS gyrotron magnet will consist of flat coils wound from commercial HTS tape, where GdBaCuO superconductor is deposited on a non-magnetic Hastelloy substrate for increased mechanical strength. Different design approaches will be presented, along with experimental results showing magnetic field strengths of up to 17 T. During the experiments, the HTS coils are submerged in a bath of liquid helium inside a cryostat and current is supplied to the system through a pair of current leads. These leads are designed to continuously carry current from room temperature to 4.2 K, while limiting liquid helium consumption.

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#### DEPENDENCE OF PHOTOCHEMICALLY INDUCED DYNAMIC NUCLEAR POLARIZATION ON WAVELENGTH, LIGHT INTENSITY AND MAGNETIC FIELD

CIDNP and ONP (incl NV centers), Transport of hyperpolarization, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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Photochemically induced dynamic nuclear polarization (photo-CIDNP) is a powerful and widely used technique in physics, chemistry and biology. It allows for the investigation of the molecules by exploiting the transfer of electron spin polarization to the surrounding nuclei upon photoexcitation of the sample.

Photo-CIDNP can be used to study a wide range of biological systems, including proteins, nucleic acids etc.[1-2]. Furthermore, the main advantage of photo-CIDNP is that it can provide a much higher sensitivity improving other techniques, such as nuclear magnetic resonance (NMR). It is particularly effective for polarizing low-concentration samples in zero to ultra-low field (ZULF) conditions.

While more systems can now be polarized using light irradiation, previous studies primarily employed either nontuneable sources like light-emitting diodes or lasers or white light [2-4]. In our research, we examined the amplitude dependence of photo-CIDNP on wavelength, light intensity, and magnetic field. An optical condenser with a xenon lamp served as the light source, with light intensity adjusted using neutral density filters. We used a set of 10-nmwidth band-pass interference filters, enabling wavelength selection in the range of 350 to 800nm with 50nm increments. To generate a tuneable and homogeneous magnetic field of up to 150mT, we employed a Halbach array system described in [5]. The overall polarizer setup was compact and user-friendly.

Nuclear polarization was measured using a NMR spectrometer of "Magritek's Spinsolve". As model samples, we used the same system as described in [6-7]: a solution containing 5mM benzoquinone and 0.5mM tetraphenylporphyrin dissolved in a mixture of 70% deuterated chloroform and 30% acetic acid.

The dependence of the photo-CIDNP signal on wavelength was compared with the absorption spectra of the same solution for quantifying polarization efficiency.

Additionally, we observed photo-CIDNP for the first time in low fields (below 150mT) in water solutions of riboflavin (0.5mM) mixed with either tyramine, tyrosine, or methionine (7mM each) using the setup. For each sample, we measured the dependences of photo-CIDNP signals on wavelength and magnetic field.

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#### NEW INSIDES FROM LIQUID-STATE DNP PERFORMED AT 9.4 T

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Very early it was recognized that the Overhauser effect1, first observed in metals, is also effective in liquid solutions2, allowing to transfer electron spin polarization from radicals to nuclear spins of diamagnetic target molecules in solution. Theoretical descriptions based on the translational diffusion and rotation of the radical and target molecules in solution have been developed to describe the Overhauser DNP polarization transfer mechanism in liquids3. Also very early on, it was recognized that the solid DNP mechanism can compete against the Overhauser effect in viscous liquids4. These models have been used at low magnetic fields (< 1.5T) to determine molecular diffusion rates and rotational correlation times. DNP experiments performed at high magnetic fields (9.4 T) allowed to critical review these parameters and to get some new and interesting insides in the polarization transfer and polarization dispersion mechanism in liquid media. In this presentation an overview over the new findings and interpretations resulting from DNP at and above room temperature at 9.4 T.

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Т 17

#### OBSERVATION OF QUADRUPOLAR NUCLEI NEAR SURFACES USING HIGH-RESOLUTION MAS DNP AND ULTRA-HIGH-FIELD NMR

MAS-DNP

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First observation of surface 33S nuclei in natural abundance (0.76%) using MAS DNP.

The surfaces of inorganic materials play a key role in numerous applications, such as catalysis, biomaterials, cements, and optoelectronics. As a local characterization technique capable of providing atomic resolution, solid-state NMR can afford unique insights into the molecular-level structure of inorganic surfaces. However, low intrinsic sensitivity of solid-state NMR often limits the characterization of surfaces due to the small fractions of the nuclei located near the surfaces.

Dynamic nuclear polarization (DNP) under magic-angle spinning (MAS) is a powerful technique to enhance the NMR signals of spin-1/2 nuclei, such as 13C, 15N or 29Si, near surfaces. Nevertheless, this technique is still challenging to apply for the observation of quadrupolar nuclei, such as 11B, 17O, 27Al, 33S and 67Zn, which represent over 74% of NMR-active isotopes. A first obstacle is the difficulty to transfer efficiently the DNP-enhanced 1H magnetization to quadrupolar nuclei since cross-polarization under MAS lacks robustness and efficiency for quadrupolar nuclei. Furthermore, the NMR spectra of quadrupolar nuclei often exhibit low resolution since their

NMR transitions are broadened by the quadrupolar interaction.

We recently introduced an efficient method based on through-space INEPT to transfer the DNP-enhanced 1H magnetization to quadrupolar nuclei [1]. We report here how we leveraged this technique to detect natural abundance NMR signals of 33S and 67Zn nuclei near the surfaces of ZnS quantum dots [2]. These quadrupolar nuclei are challenging to detect owing to their low gyromagnetic ratios, low natural abundances and large quadrupolar interactions. To the best of our knowledge, it represents the first example of 33S DNP-NMR experiments reported in the literature. These DNP results combined with ultra-high-field NMR experiments (up to 35.2 T) and DFT calculations provided unique information on the structure of ZnS quantum dots and the presence of S vacancies. The through-space INEPT transfer was also combined with multiple-quantum MAS (MQMAS) sequence to acquire high-resolution spectra of 11B, 17O and 27Al nuclei near surfaces [3]. This experiment was applied to unravel the structure of B, O and Al surface sites of quantum dots and nanocatalysts.

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### ACROSS CITIES DDNP: STRATEGIES AND CHALLENGES TO MAKE HYPERPOLARIZATION TRANSPORTABLE.

Transport of hyperpolarization

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T 18

## Isometric view (A) and section view (B) of the NMR capable compact HP sample transportation device (H x $W \times T = 55$ cm x 25cm x 25cm).

As of today, dissolution Dynamic Nuclear Polarization (dDNP)[1] is the only clinically available hyperpolarization technique for 13C-MRI. Despite the clear path towards personalized medicine that dDNP is paving as an alternative and/or complement to PET, the technique struggles to enter everyday clinical practice. One of the reasons is that, differently from PET, hyperpolarized (HP) MR-contrast agents cannot be transported and have to be produced on-site, using expensive and technically demanding hardware (i.e. the polarizer). The culprits are the same unpaired electron spins used, in the first place, to generate the hyperpolarization.

From some years we are working to make hyperpolarization transportable. The idea behind builds on the use of photo-induced thermally-labile free radicals.[2] As the paramagnetic molecules decompose (quench) at around 190K it is possible to remove them already in the solid state inside the polarizer while retaining the DNP-induced hyperpolarization and increasing the half-life of the sample by 1000-fold.[3] By means of thorough investigation of relaxation processes and design of purpose built hardware [4], we succeeded in demonstrating the first across cities in vivo dDNP experiment for 2 compounds: the metabolic probe [U-13C, d7]glucose and the perfusion agent [1-13C, U-d]HPO01. Thanks to an initial 13C solid-state polarization of 50%, limited losses during the hyperpolarized sample radical quenching and extraction procedure, and a relaxation time of 20 h at transport conditions we managed to deliver to the site of use, 5 h after extraction of the solid sample, hyperpolarized solutions with a liquid-state polarization level close to 30%. We also discuss challenges related to the hyperpolarization and transport of [1-13]C pyruvate and strategies to circumvent them.

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1 19

#### METHODS AND INSTRUMENTS FOR HIGH-FIELD MAS DNP TOWARD INTRACELLULAR STRUCTURAL BIOLOGY

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Sensitivity of MAS NMR has been dramatically improved by the advent of the high-field DNP techniques. Especially, we have shown that implementing DNP at ultra-low temperatures (ULT, T  $\ll 100$  K) using helium gas greatly improves the DNP efficiency at high field, high-resolution conditions (i.e., B0  $\gg 10$  T). A key technological breakthrough therein comprises the closed-cycle helium gas circulation (CHC) MAS system and dedicated DNP probe [1,2], that maintains the sample spinning at 20 K ( $\pm$  0.1 K) and 8 kHz ( $\pm$  0.003 kHz) for weeks without consuming any helium. The long-term stability and its seamless temperature controlling ability between 20 and 200 K has enabled a number of applications in biological [3] and material sciences [4], and also contributed to understanding the mechanistic origin of the Overhauser DNP [5]. The system is also combined with a cryogenic signal detection system for the thermal noise suppression, being cooled "for free" using the cold (~40 K) return helium gas on its way back to the CHC compressor [6]. Based on these instruments, the net sensitivity gain of over 4000 is achievable at T = 30 K, B0 = 16.4 T.

Beyond the sensitivity improvement, we have been exploring new DNP methods e.g., for the nano space-selective observation [7] and background signal suppression, both of which being the key for looking at target molecules within unpurified mixture samples. We also demonstrate nano-diamond is a promising polarizing agent for MAS DNP on proteins at 16.4 T in strongly reducing environments such as within biological cells. These basic technical advances combined should open up a new avenue to highly sensitive and target molecule-selective protein structural analysis in biological cells. In the presentation, we will discuss the latest results on such methods, instrument and applications.

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#### ROUTINE HYPERPOLARIZED 129XE NMR UTILIZING A BENCHTOP SPECTROMETER

General Instrumentation, Optical pumping & SEOP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation

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Owing to the large signal enhancement independent of the Zeeman field strength, it is obvious to combine hyperpolarization with low-cost benchtop NMR systems as shown for DNP and PHIP [1]. However, to our knowledge just the basic usability of hyperpolarized 129Xe gas (hypXe) applying an elaborate handling on a benchtop NMR spectrometer was demonstrated [2]. Here, the instrumentation, and efficient operation of a continuous flow 129Xe polarizer together with a commercial benchtop spectrometer is presented, allowing routine hypXebenchtop NMR as demonstrated in presentation [3].

A prototype hypXe SEOP polarizer (alike [4]) was adapted to feed the hypXe gas stream at the time of demand into an NMR sample tube, residing within the benchtop spectrometer. Basically, a continuous gas stream (Xe-N2-He mixture in adjustable partial pressures) is blend by three mass-flow controllers and first lead through the 70 ml optical pumping cell at a total flow rate of typically 35 ml/min; from the cell's outlet the gas stream is fed via a ~2.5 m long, 2 mm ID PFA tube to right above the benchtop spectrometer (lasting  $\sim 13$  s). There, a pneumatically driven, NMRconsole controlled PFA membrane valve allows the gas flow either only to by-pass or to partially pass through the NMR sample tube via another ~0.6 m long, 1 mm ID PFA tube and finally two ~15 cm long, 200 um ID capillaries. The flow rate of gas being fed into the sample is set by the pressure difference held by a back-pressure regulator  $(\sim 3.1 \text{ bar})$  sitting in the bypass tube before merging with the sample outlet-tube where the gas pressure is held at 3 bar. As common for all hyperpolarized media the transport via magnetic field gradients may give rise to polarization losses, particularly when entering the well-shielded Zeeman field of a benchtop spectrometer. Thus, for absolute 129Xe polarization determination flame sealed NMR tubes containing precisely known xenon pressures were produced as reference standard. Applying those and a very lean, 1 mbar xenon partial pressure in the gas stream we measured 129Xe polarizations larger than 50% within the benchtop spectrometer. This implies that the overall loss by the transfer from the polarizer to the NMR sample could not be larger than 50% (more probable 1/3) and demonstrates the high-quality performance of the instrumentation setup, furthering future widespread applications of hpXe benchtop NMR with the potential to be integrated in much more compact systems.

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#### BETTER BIRADICALS FOR SIGNAL ENHANCED SSNMR DNP: A CHEMICAL AFFAIR

Triplet DNP

Gilles Casano (1), Amrit Venkatesh (2), Gabriele Stevenato (2), Yu Rao (2), Lorenzo Niccoli (3,4), Federico De Biasi (2), Frederic A. Perras (5), Dominik Kubicki (2), Hakim Karoui (1), Maxim Yulikov (6), Gunnar Jeschke (6), Moreno Lelli (4), Anne Lesage (3), Lyndon Emsley (2), Olivier Ouari (1)

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#### better DNP through Chemistry

Dynamic nuclear polarization (DNP) is a consensus strategy to overcome the well-recognized sensitivity limitations of nuclear magnetic resonance (NMR) experiments. In particular, DNP-induced sensitivity enhancements have been demonstrated in magic-angle-spinning (MAS) NMR experiments on various systems in 1D and 2D solid-state NMR experiments that are otherwise difficult or unfeasible, even with isotope labeling. In DNP experiments, the comparatively high electron spin polarization of the polarizing agents (PAs) is transferred to nuclear spins via microwave irradiation. The source of unpaired electrons is vital for efficient DNP and has been the subject of intense recent scrutiny. Over the past decade, a number of design criteria for efficient PAs have been identified and implemented.

In DNP, polarization is typically transferred from unpaired electrons of a PA to nearby proton spins. In solids, this transfer is followed by the transport of hyperpolarization to the bulk of the sample via 1H-1H spin diffusion. The efficiency of these steps is critical to obtain high sensitivity gains with DNP, but the pathways for polarization transfer in the region near the unpaired electron spins are unclear. Here we report a series of seven deuterated and one fluorinated TEKPol biradicals to probe the effect of deprotonation on MAS DNP at 9.4 T. Additionally, we introduce and demonstrate the importance of a new design parameter related to the local geometry around the unpaired electron. We show that DNP performance is dramatically affected, at both 9.4 and 21.15 T, by changes in local conformation around the unpaired electron in mono- and dinitroxides, for otherwise identical constitution irrespective of the radical concentration.



#### A 2H APPROACH TOWARDS INVESTIGATION OF METHYL DYNAMICS UNDER DNP

#### MAS-DNP, Loss of hyperpolarization & relaxation

Thomas Biedenbänder (1,2), Victoria Aladin (1,2), Liliya Vugmeyster (3), Björn Corzilius (1,2,4)

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A 2H approach for measuring methyl dynamics under DNP conditions

Methyl NMR studies have become highly popular in NMR spectroscopy during the last decades. The fast threefold reorientation of the methyl group around its symmetry axis (H3C-C) yields advantageous relaxation properties and thus well-resolved NMR spectra.[1] Moreover, it was recently shown that the three-fold reorientation is still active under DNP conditions being exploited in SCREAM-DNP (Specific Cross Relaxation Enhancement by Active Motions under DNP).[2] Here, the cross-relaxation-promoting methyl dynamics drive the polarization transfer from the hyperpolarized 1H spins to 13C. The specifically hyperpolarized methyl-13C can then be used, for example, for extracting information about the interface between an RNA and a protein.[3]

This study aims to gather a more detailed molecular understanding of methyl dynamics at low temperatures, particularly their behavior under DNP conditions, which have not been extensively described so far. Therefore, selectively deuterated methyl groups of methyl-bearing molecules are used as a model system to investigate methyl dynamics inside a glassy matrix and in the presence of polarizing agents. The applied 1H 2H CPMAS yields high DNP enhancements facilitating the determination of 2H-R1 relaxation rates at a range of 100 to 165 K. Our results suggest a distribution of 2H R1 relaxation rates represented by a stretched exponential, as shown in wetted protein powder,[4] yielding an activation energy for the three-fold reorientation of 3 kJ/mol in the case of ethanol-d3. However, the presence of the radical impacts the underlying spectral density of the measured relaxation rate as observed by comparison of a doped with an undoped sample. This indicates the necessity to establish a general and reliable approach to measure methyl dynamics under DNP.

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### RADICAL PAIR MAGNETORECEPTION: HYPERPOLARIZED BIRDS?

Peter Hore (1)

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Small migratory songbirds are extraordinary navigators: weighing less than 30 g, they fly thousands of kilometres between their breeding and wintering grounds, alone and at night. To do so they use the sun and the stars, olfaction and landmarks, but it is clear that they can also perceive the direction of the Earth's magnetic field. Despite more than 50 years of research, the biophysical mechanism of this remarkable magnetic sense remains obscure. In this lecture, I will discuss the proposal that the birds' magnetic compass relies on a quantum mechanism in their eyes.

T 23

Specifically, the unique properties of light-induced, hyperpolarized radical pairs in cryptochrome proteins in photoreceptor cells could allow chemical sensing of magnetic interactions orders of magnitude weaker than previously thought possible.

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### PYRROTRIPOL AND DEUTERATED ASYMPOL FROM THE VIEWPOINT OF SIMULATIONS AND EXPERIMENTS

MAS-DNP

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Molecular Dynamics shows PyrroTriPol's bridge is rigid.

Magic Angle Spinning Dynamic Nuclear Polarization (MAS-DNP) enhances solid-state NMR experiments, making possible the study of systems where the nuclear spin of interest is low in concentration [1]. These experiments often rely on biradicals to generate fast and high 1H polarization buildup. Whereas simulating large spin systems to understand MAS-DNP has enabled great progress, there is still much research to design more efficient biradicals for use at very high magnetic fields. Additionally, there are still unanswered questions; notably, what is the role of

protons on the biradicals and how 1H does hyperpolarization spread from them to the 1H of the sample.

Hetero-biradicals, e.g. Trityl-Nitroxides or BDPA-Nitroxides, are efficient for DNP at high fields; however, they present difficult synthetic routes, moderate stabilities, and the current chemical bridges can limit DNP efficiency [2,3]. We thus designed a new Trityl-nitroxide family, the PyrroTriPols [4], with two goals: (i) to be effective DNP agents for both materials science and biological uses, and (ii) to have synthetic scalable protocols that are high-yield and high-purity. After an in silico screening, we found that the piperazine linker strikes a good balance between Trityl-nitroxide distance and rigidity, as assessed by MD calculations and EPR. PyrroTriPol and PyrroTriPol-OMe, soluble in water and organic solvents respectively, demonstrated very high DNP efficiency at all fields tested. In addition, both radicals were found to work well with low microwave amplitudes, making them candidates for low-power DNP spectrometers.

In a separate study, the roles of the protons in the biradicals were explored; notably, in the case of AsymPol is of great interest, since it has the shortest polarization time Tb's [5]. Simulations were used to analyze how the hyperpolarization spreads from the biradicals to the sample and revealed that, unlike other biradicals, AsymPol directly transfers spin polarization to 1H in the surrounding solvent shells. Numerical simulations thus predict that deuterated forms of AsymPol lead to higher hyperpolarization and unchanged Tb, both of which were checked experimentally. This work opens new possibilities for development of even better biradicals, which feature stronger e-e coupling, better relative g-tensor orientations, and optimal deuteration levels.

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### Nobuhiro Yanai yanai@mail.cstm.kyushu-u.ac.jp



### TRIPLET DYNAMIC NUCLEAR POLARIZATION OF BIO-RELEVANT MOLECULES BY NEW POLARIZING AGENTS

Triplet DNP

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#### Mateirals chemistry of triplet-DNP

Nuclear magnetic resonance (NMR) spectroscopy and magnetic resonance imaging (MRI) are powerful and versatile methods in modern chemistry and biology fields. Nevertheless, they suffer from intrinsically limited sensitivity due to the low nuclear spin polarization at ambient temperature. One of the promising methods to overcome this limitation is dynamic nuclear polarization (DNP) that transfers spin polarization from electrons to nuclei. In particular, DNP based on photo-excited triplet (triplet-DNP) is promising, since it allows the hyperpolarization at room temperature.[1-3] In typical scheme of triplet-DNP, the spin-selective intersystem crossing (ISC) produces the large electron spin polarization in the excited triplet state sublevels, and this polarization is effectively transferred to nuclear spins by a microwave irradiation for satisfying Hartmann-Hahn condition, so-called integrated solid effect (ISE).

While much efforts have been devoted to obtaining the large nuclear polarization based on triplet-DNP, the application of triplet-DNP to biological systems has been challenging. Towards biological applications, we have proposed to introduce materials chemistry into the field of triplet-DNP.[4] In this talk, we will highlight some recent examples such as the hyperpolarization of drug molecules in nanoporous metal-organic frameworks (MOFs),[5,6] the polarization transfer from nanocrystals to water,[7] and hyperpolarization using singlet fission-derived quintet multiexcitons.[8] In addition, we will discuss the new design guidelines of triplet polarizing agents to achieve high nuclear polarization even in unoriented samples, which is critical to various biological applications.[9,10]

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### MARVELS AND CHALLENGES OF LC-PHOTO-CIDNP NUCLEAR-SPIN HYPERPOLARIZATION IN LIQUIDS

Silvia Cavagnero (1), Shapla Ummay Mahfuza (1), Siyu Li (1), Hanming Yang (1)

(1) University of Wisconsin-Madison (USA)



Low-concentration photochemically induced dynamic nuclear polarization (LC-photo-CIDNP) is a powerful emerging technology for the hyperpolarization of aromatic amino acids in solution, both in isolation and within proteins. In this talk, the basic aspects of this LED-enhanced NMR approach will be introduced, including recent advances that further increase its capabilities, as well as remaining challenges. Among the advantages: the presence of low-µM concentrations of the reductive radical quencher vitamin C enables LC-photo-CIDNP data acquisition for a significantly longer time than ever possible before. In addition, biomolecules carrying a quasi-isolated spin pair (QISP), e.g., a selectively labeled Trp isotopolog, display unprecedented LC-photo-CIDNP enhancements, due to the ad hoc elimination of deleterious LC-photo-CIDNP cancellation effects. Conveniently, the combination of the above advances leads to additional increases in NMR sensitivity in liquids, enabling NMR data collection in the low nanomolar range in less than a minute at 600 MHz. Very high enhancements are also gained at extremely low applied magnetic fields in the context of field-cycling. Conveniently, the LC-photo-CIDNP technology works well for the structural analysis of amino acids and proteins in buffered solution or in highly complex media, including cell-like milieux. The above exciting advantages pave the way to a variety of applications targeting biological questions in situ, at extremely low, and physiologically relevant, sample concentrations. Remaining challenges include the need to freshly prepare NMR samples, preferably in situ, and the selective nature of the technology, which works well only for solvent-exposed aromatic amino acids. Strategies to overcome the above challenges will be discussed during the presentation.



#### DYNAMIC NUCLEAR POLARIZATION WITH POLARIZING MATRICES: FROM SILICA AND EPOXY TO CONDUCTIVE POLYMERS

Dissolution/Melt DNP, Other hyperpolarization methods

Léa Bellier (1), Nathan Rougier (1), Charlotte Bocquelet (1), Ewoud Vaneeckhaute (1), Guillaume Verhaeghe (1), Théo El Daraï (1,2), Huu-Nghia Le (1,3), Laurent Veyre (3), Chloé Thieuleux (3), Damien Montarnal (2), Roberto Melzi (4), Daniel Banks (4), James Kempf (4), Quentin Stern (1), Sami Jannin (1)

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## Emeraldine base - EPR silent



Chemical structure of two forms of PANI polymers, the emeraldine base and salts and the microwave spectrum of PANI with ≈100 µmol.g-1 of radical at 1.6 K and 7 T.

T 27

Hyperpolarization by dissolution dynamic nuclear polarization (dDNP)1 has recently evolved into a robust method providing a decisive solution to this lack of sensitivity as it enhances nuclear spin polarization - and therefore sensitivity - by up to four orders of magnitude. High electron spin polarization is transferred to nuclear spins of interest in the frozen state. It is then followed by a 'single shot' irreversible melt, dilution, and transfer to a room-temperature liquid-state NMR apparatus. This strategy is compatible with a few applications in which exhaustibility and pollution can be accommodated.

However, most NMR applications are multi-scan by essence and incompatible with hyperpolarization by dDNP. Indeed, NMR experiments quasi-systematically rely on multi-scan approaches. This situation is untenable, preventing numerous laboratories and industries to greatly benefit from this hyperpolarization strategy. The bottleneck for producing pure and inexhaustible hyperpolarized solutions comes from the very nature of the instrumental and sample formulation design, so far conceptualized and conceived for 'single-shot', contaminated, and diluted experiments.

Here we will review some of the most recent work on hyperpolarizing matrices, opening the way to a radically different approach that aims at producing pure and inexorable streams of hyperpolarization on arbitrary complex mixtures. This approach consists in a physical separation of the polarizing matrices from the solution to be polarized2,3 which enables dilution-free melting. More recently, we started using conductive polyaniline polymers (PANI). We report polarization of up to  $\approx 5\%$  with astonishingly fast build-up time constants of  $\approx 20$  s and a surprising variety of DNP mechanisms. Most interestingly, PANI display the astonishing property that the electron spins can be hyperpolarized beyond Boltzmann by chirality-induced spin selectivity (CISS).4

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#### MICROSCALE NV-NMR ON A CHIP LOOKING FOR HYPERPOLARIZATION METHODS

General Instrumentation, Applications

Dominik B. Bucher (1)

(1) Technical University of Munich



The nitrogen-vacancy (NV) point defect in diamonds is a novel type of quantum sensor that allows for the detection of magnetic fields on unprecedented length scales. This technique enables the measurement of magnetic resonance signals on the nanoscale, down to a single electronic or nuclear spin [1]. We utilize this method to perform NMR spectroscopy on the microscale for lab-on-a-chip applications or future single-cell studies [2]. However, despite the NV-sensor's exceptional volume sensitivity, the concentration sensitivity remains relatively low. To address this limitation, we have successfully implemented different hyperpolarization methods, ranging from Overhauser [3] to parahydrogen [4] based schemes. However, these methods are not readily applicable to biological samples or may lack sufficient throughput for lab-on-a-chip applications. In the outlook of our presentation, we will discuss the hyperpolarization methods criteria that are required for an efficient combination with NV-diamond NMR.

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## **PROGRAM OF THE ROUND-TABLES**

## Monday 25th September

## Mon, 14:00

**Table 1**, **RT 65**, Increasing the hyperpolarization level on fully biocompatible ParaHydrogen

 polarized pyruvate *Francesca Reineri*

**Table 2**, **RT 78**, Kinetic study of the action of glucose-6-phosphate dehydrogenase onhyperpolarized glucose-6-phosphate using dissolution Dynamic Nuclear Polarization (D-DNP)*Mehdi Soussi-Therond* 

**Table 3**, **RT 70**, 200 GHz Single Chip Dynamic Nuclear Polarization Microsystem Nergiz SahinSolmaz

**Table 4**, **RT 24**, In Vivo Metabolic Imaging of [1-13C] Pyruvate-d3 Hyperpolarized by ReversibleExchange with Parahydrogen. *Philipp Groß* 

**Table 5**, **RT 17**, Characterization of micro- and mesopores of ETS-10-based titanosilicatecatalysts by hyperpolarized Xe-129 NMR *Muslim Dvoyashkin* 

## Mon, 14:20

 Table 1, RT 52, Design and application of photo-CIDNP molecular probes Koki Nishimura

**Table 2**, **RT 92**, Hyperpolarizing nuclear spins using parahydrogen and metal-free catalysts:MF-PHIP Vladimir V. Zhivonitko

**Table 3**, **RT 59**, Combining dDNP with GIPAW calculation to determine the structure of shortlived intermediates. *Christopher Pötzl*

**Table 4**, **RT 28**, Polarization Transfer Rates in Endogenous Metal Ions DNP Daniel Jardon-Alvarez

**Table 5**, **RT 30**, A 14 T / 7 T DNP / EPR Spectrometer for the Investigation of Dynamic Nuclear

 Polarization Mechanisms *Ilia Kaminker*

## Mon, 14:40

**Table 1**, **RT 53**, Relaxation mechanisms for efficient DNP in the liquid state at high magneticfields *Tomas Orlando* 

**Table 2**, **RT 27**, A combined pyruvate probe of 2H and hyperpolarized 13C for metabolic brain MR imaging *Kristina Pilgaard Jacobsen* 

**Table 3**, **RT 87**, A Mobile 3D Cell Culture System for Longitudinal Intracellular Metabolic

 Profiling via Hyperpolarized 13C-NMR *Thomas Benjamin Wareham Mathiassen*

**Table 4**, **RT 60**, Spying on parahydrogen-induced polarization transfer using a half-tesla benchtop MRI and hyperpolarized imaging enabled by automation *Andrey Pravdivtsev* 

 Table 5, RT 3, Systematic investigation of the serial polarization transfer due to combination of cross-relaxation and rotational resonance under MAS DNP Edvards Roberts Bensons

## Mon, 15:00

**Table 1**, **RT 22**, Cryogenic and dissolution DNP on γ-irradiated and impregnated powder samples *Angeliki Giannoulis* 

 Table 2, RT 46, Over 20% 13C-Hyperpolarization and Fast Imaging of Ethyl-[1-13C]-Acetate-d6

 and Ethyl-[1-13C]-Pyruvate-d6 using SAMBADENA Obaid Mohiuddin

**Table 3**, **RT 29**, Relaxation and Exchange of Nuclear Hyperpolarization at Low Temperature

 and Field *Michael Jurkutat*

**Table 4**, **RT73**, Control of magneto-optical properties of cobalt-layers by adsorption of  $\alpha$ -helical polyalanine self-assembled monolayers *Georgeta Salvan* 

**Table 5**, **RT 89**, Liquid-state two-dimensional 13C-13C correlation NMR enhanced byOverhauser dynamic nuclear polarization at 9.4 Tesla Luming Yang

### Mon, 15:20

 
 Table 1, RT 31, 13C imaging of pyruvate with SABRE-SHEATH and LIGHT-SABRE at Ultra-Low field Nicolas Kempf

**Table 2**, **RT 64**, High-field non-hydrogenative PHIP (HF-nhPHIP) for the analysis of human and veterinary urine samples *Nele Reimets*

**Table 3**, **RT 2**, Fully endogenous molecular probes for imaging brain metabolism *Fatemeh Anvari Vind*

**Table 4**, **RT 41**, Liquid-state 13C Overhauser dynamic nuclear polarization at 9.4 Tesla MarcelLevien

Table 5, RT 47, Solid State photo-CIDNP NMR applying biomimetic dyads Guzel Musabirova

### Mon, 16:10

**Table 1**, **RT 63**, Exploring the scope of nhPHIP hyperpolarization in metabolite analysis in human biofluids *Indrek Reile*

**Table 2**, **RT 35**, SABRE hyperpolarized 13C pyruvate-d3 via Spin-Lock Induced Crossing(SLIC) at low-fields enables in vivo metabolic imaging *Stephan Knecht* 

**Table 3**, **RT 51**, Investigation of 13C Static DNP of P1 Centers in Diamond at 13.8 T and 6.9 T using ELDOR and Pulsed EPR Experiments *Orit Nir-Arad* 

**Table 4**, **RT 90**, In vivo detection and imaging of aminopeptidase activity through the rational design of hyperpolarized molecular probes utilizing dissolution dynamic nuclear polarization. *Hiroyuki Yatabe* 

**Table 5**, **RT 40**, High-field solid-effect DNP in viscous liquids using narrow EPR line polarizingagents Andrei Kuzhelev

## Mon, 16:30

**Table 1**, **RT 82**, Low-field NMR spectroscopy with in-situ parahydrogen hyperpolarisation DanielA. Taylor

 Table 2, RT 43, Portable Hyperpolarized Xe-129 Apparatus with Long-Time Stable Polarisation

 Marcel Meinhart

**Table 3**, **RT 93**, Dynamic nuclear polarization of inorganic halide perovskites, *Dominik Kubicki* **Table 4**, **RT 1**, Exploiting the Electron Spin: Expanding the MAS DNP Experimental Reach using a Frequency-Agile Gyrotron *Nicholas Alaniva* 

**Table 5**, **RT 20**, Room Temperature Overhauser Dynamic Nuclear Polarization on OrganicSemiconductors Yao Fu

### Mon, 16:50

**Table 1**, **RT 62**, Partially Negative Line of Orthohydrogen Resonance in Signal Amplification byReversible Exchange Tomasz Ratajczyk

**Table 2**, **RT 79**, Importance of orientation control of polarizing agents in Triplet DNP Kenichiro

 Tateishi

**Table 3**, **RT 6**, Hyperpolarized 13C-enriched pyruvates by SABRE in acetone *Oksana Bondar* **Table 4**, **RT 39**, Stabilization of a flavoprotein for solid-state photo-CIDNP MAS NMR at room temperature by embedding in a glassy sugar matrix *Patrick Kurle-Tucholski* 

**Table 5**, **RT 69**, Towards Tabletop Recyclable Hyperpolarization with a Compact Freeze, Melt, and Flow DNP Polarizer *Nathan Rougier* 

### Mon, 17:10

**Table 1**, **RT 66**, Large 31P-NMR enhancements in liquid state dynamic nuclear polarization

 *Maik Reinhard*

Table 2, RT 86, Rate equations in hyperpolarized NMR Gevin Von Witte

**Table 3**, **RT 37**, Advantages of photo-SABRE: long lived hyperpolarization of trans 15N2azobenzene is formed by combining SABRE of cis-isomer with in situ photoisomerization in ZULF *Vitaly Kozinenko* 

**Table 4**, **RT 18**, An introduction to the radiation detection MRI: the Gamma-MRI project.*Katarzyna Dziubinska-Kuehn* 

**Table 5**, **RT 38**, Nanostructure analysis of composite materials and multi-layer films by spincontrast-variation neutron scattering and reflectivity *Takayuki Kumada*

## **Tuesday 26th September**

## Tue, 14:00

**Table 1**, **RT 15**, Improved polarizing agents and cost-effective sustainable cryogenic HeliumMAS for High Field Dynamic Nuclear Polarization Gaël De Paëpe

**Table 2**, **RT 83**, Exploring the solid-state-photo-CIDNP effect in artificial poly-L-proline based,flavin-aminoacid diads *Tobias Theiss* 

**Table 3**, **RT 4**, Photo-CIDNP enables 19F MRI at 0.6 T with spatially-resolved detection of subnmol of amount of the anti-COVID19 drug Favipiravir. *Johannes Bernarding* 

 Table 4, RT 81, Continuous real-time detection of hyperpolarized 1H and 13C nuclear spins in liquids *Michael Tayler*

Table 5, RT 44, Automated Bullet-Dynamic Nuclear Polarization Masoud Minaei

## Tue, 14:20

Table 1, RT 73, break

**Table 2**, **RT 53**, Relaxation mechanisms for efficient DNP in the liquid state at high magneticfields *Tomas Orlando* 

**Table 3**, **RT 10**, Off-the-shelf Gd(III) compounds as efficient high-spin metal ion polarisingagents for magic angle spinning dynamic nuclear polarisation *Daniel Cheney* 

Table 4, RT 34, 77Se SABRE polarization via scalar network coupling in ZULF *Alexey Kiryutin* Table 5, RT 0, break

## Tue, 14:40

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Table 4, RT 86, Rate equations in hyperpolarized NMR Gevin Von Witte

Table 5, RT 49, Altered metabolism in antibiotic-tolerant bacteria Alexandra Neergaard Zahid

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**Table 1 RT 76** Dynamic view of the solid-state DNP effect in solids and liquids *Deniz Sezer***Table 2, RT 84**, Monitoring a phase transition of calcium phosphate by dDNP NMR *ErtanTurhan* 

**Table 3**, **RT 56**, Using MEOP hyperpolarized 3He for improving precision in magnetic fluxdensity measurement *Wiebke Pohlandt* 

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 Table 3, RT 75, Quantitative 129Xe HyperCEST Spectroscopy with Competitive Guests

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**Table 5**, **RT 32**, Realisation of a Rb-Xe comagnetometer for noble-gas spin quantum memoriesWolfgang Kilian

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**Table 2**, **RT 20**, Room Temperature Overhauser Dynamic Nuclear Polarization on OrganicSemiconductors Yao Fu

 Table 3, RT 26, Transportable reservoir of nuclear polarization to enhance solution-state NMR signals Patrick Hautle

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**Table 2**, **RT 7**, Human Serum Albumin as Magnetic Resonance Imaging Overhauser DNP SpinProbe Carrier System *Friedemann Bullinger* 

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**Table 2**, **RT 57**, PHIP over heterogeneous catalysts – the role of carbide phases and ortho-para conversion *Ekaterina Pokochueva*

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**Table 5**, **RT 60**, Spying on parahydrogen-induced polarization transfer using a half-teslabenchtop MRI and hyperpolarized imaging enabled by automation Andrey Pravdivtsev

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 Table 2, RT 85, Quantum-chemical studies in spin physics Juha Vaara

**Table 3**, **RT 16**, DNP probehead for liquids at 9.4 Tesla with improved temperature stabilityVasyl Denysenkov

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**Table 2**, **RT 30**, A 14 T / 7 T DNP / EPR Spectrometer for the Investigation of Dynamic Nuclear

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**Table 2**, **RT 25**, Nanomolar detection of biosensors with hyperpolarized 129Xe applying abenchtop spectrometer Samira Gulich

**Table 3**, **RT 23**, Dynamics on the surface via electron and nuclear spin probes *Bulat Gizatullin***Table 4**, **RT 42**, Probing minority components in microplastic via MAS-DNP NMR spectroscopy*Anika Mauel* 

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**Table 1**, **RT 11**, Hyperpolarized Samples for Large Animal Experiments with Next-GenerationPolarizers Ditte Bentsen Christensen

**Table 2**, **RT 35**, SABRE hyperpolarized 13C pyruvate-d3 via Spin-Lock Induced Crossing(SLIC) at low-fields enables in vivo metabolic imaging *Stephan Knecht* 

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**Table 4**, **RT 40**, High-field solid-effect DNP in viscous liquids using narrow EPR line polarizingagents Andrei Kuzhelev

 Table 5, RT 68, Setup of time-resolved photo-CIDNP MAS NMR experiments with a pulsed nanosecond laser Ronja Rößler

## **Thursday 28th September**



#### Nicholas Alaniva

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#### EXPLOITING THE ELECTRON SPIN: EXPANDING THE MAS DNP EXPERIMENTAL REACH USING A FREQUENCY-AGILE GYROTRON

#### MAS-DNP

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 (2) Universität Rostock, Institute of Chemistry, Department Life, Light & Matter, Rostock, Germany
 (3) Universität Osnabrück, Department of Physics, Osnabrück, Germany
 (4) University of Iceland, Department of Chemistry, Science Institute, Reykjavik, Iceland

Dynamic nuclear polarization (DNP) is a powerful technique that has unlocked many low-sensitivity systems, ranging from biological membranes to inorganic surfaces, for investigation with nuclear magnetic resonance (NMR). Here, we present advancements in DNP technology and application of that technology to novel systems - aimed toward improving sensitivity of magnetic resonance experiments by controlling the electron spin. Demonstration of methods for electron control are conducted with trityl-based radicals, as well as with the "ultra-narrow-line" electron spin-3/2 of nitrogen-endofullerenes (N@C60).

We perform all experiments at a field of 7 T, using a cryogenic magic angle spinning (MAS) apparatus capable of stable MAS DNP experiments at temperatures down to 4.2 K. DNP transfer is facilitated by microwave irradiation (198 GHz), generated by a custom frequency-agile gyrotron, and the real-time observation of the frequency response is made possible through a custom GHz-detection circuit. The frequency agility and the relatively high power output of this gyrotron allow for microsecond-control of the microwave frequency synchronized with the NMR pulse sequence. This enables "time domain" DNP, as well as optimized electron decoupling to improve sensitivity, and in the case of the latter, also resolution.

Investigations into the decoupling and the coherent control of the electron spin on different forms of the trityl polarizing agent are conducted through DNP experiments that probe the coupling of the trityl unpaired electron to 13C spins within the sample matrix, as well as 31P spins that are linked to the trityl molecule, itself. The direct linkage between the observed 31P nuclear spin and the trityl electron spin allows for better experimental characterization of the extent of control over the electron spin, and opens the door to new MAS DNP experiments that exploit the direct electron-nuclear coupling. Then, using trityl (Finland radical) and at 4.2 K and MAS, the spin-lattice relaxation of the trityl electron spin (at 40 mM concentration) is experimentally measured through the DNP-enhanced 13C NMR signal.

The application of electron decoupling is then extended beyond trityl-based radicals to the electron spin in N@C60. MAS DNP experiments show improvement in sensitivity up to 12% with electron decoupling of 13C spins in a dilute N@C60/C60 polycrystalline matrix at 90 K. This proof-of-principle demonstration is a first step toward a more widespread utilization of this powerful unpaired electron spin species.



## FULLY ENDOGENOUS MOLECULAR PROBES FOR IMAGING BRAIN METABOLISM

*General theory, General Instrumentation, Dissolution/Melt DNP, Liquid DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation* 

Fatemeh Anvari Vind (1), Thanh Phong Lê (1), Andrea Capozzi (1), Mor Mishkovsky (1)



(1) EPFL SB IPHYS LIFMET, Lausanne, Switzerland

#### DNP sweep (A) and first in vivo brain metabolism of HP glucose via UV-radicals (B)

Recent developments around photo-induced non-persistent radicals for dDNP have opened opportunities to reduce the delay between the preparation and injection of hyperpolarized substrates because filtering of potentially toxic radicals is avoided [1–3]. Moreover, the non-persistent nature of the DNP polarizing agent provides a route for making hyperpolarization transportable[4–7]. Those steps are critical for allowing the translation of hyperpolarized probes from mice to man. In particular, this technology will ease the employment of compounds with short hyperpolarized probes polarized with endogenous non-persistent polarizing agents. Here we show the first in vivo spectrum of cerebral metabolism in the mouse brain following the injection of radical-free hyperpolarized glucose solution. Challenges characterizing the technique and the scientific strategies enabling cerebral metabolism imaging will be discussed.

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#### SYSTEMATIC INVESTIGATION OF THE SERIAL POLARIZATION TRANSFER DUE TO COMBINATION OF CROSS-RELAXATION AND ROTATIONAL RESONANCE UNDER MAS DNP

MAS-DNP

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#### Serial polarization transfer

Solid-state NMR under magic-angle spinning (MAS) is a valuable tool for elucidating the structure of large biomolecules where classic liquid-phase NMR methods fail. In addition, dynamic nuclear polarization (DNP) may increase the sensitivity of MAS NMR by several orders of magnitude. Nevertheless, spectral specificity is often

sought after in order to avoid spectral crowding or facilitate resonance assignment. In this regard, SCREAM-DNP (Specific Cross Relaxation Enhancement by Active Motions under DNP) has been developed as a modern method which allows site-specific investigation of compounds using specifically introduced methyl groups. Here, hyperpolarization is first transferred from 1H to the methyl carbon by heteronuclear cross-relaxation and may then further spread to nearby carbons via spin diffusion. [1,2,3]

To expand and optimize the methodological portfolio of SCREAM-DNP, we have utilized the recoupling technique rotational resonance (R<sup>2</sup>). [4,5] R<sup>2</sup> reintroduces the dipolar interaction under MAS for homonuclear spin pairs if their chemical shift difference matches the MAS frequency; as such, no additional rf irradiation is necessary. Therefore, it may be simply applied during the build-up period of DNP in order to selectively boost spin diffusion and increase the range over which polarization spreads from the methyl group. This creates a resonance-specific serial polarization transfer pathway boosted by SCREAM-DNP which can also be combined with multi-dimensional correlation spectroscopy to selectively investigate, for example, binding sites in biomolecular complexes.

In a systematic investigation we have synthesized selectively 13C-labeled ethyl acetate as a model system to explore the compatibility and effectiveness of R<sup>2</sup> with SCREAM-DNP. By matching the R2 condition between the carbonyl and the methyl resonance we were able to boost the DNP buildup of the carbonyl resonance 10-fold. Thus, we could successfully demonstrate that these methods can be used in combination, further enabling a resonance-targeted application of SCREAM-DNP. We are currently assessing the distance dependence and its limits by investigating selectively labelled peptides of various lengths.

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#### PHOTO-CIDNP ENABLES 19F MRI AT 0.6 T WITH SPATIALLY-RESOLVED DETECTION OF SUB-NMOL OF AMOUNT OF THE ANTI-COVID19 DRUG FAVIPIRAVIR.

R I 4

CIDNP and ONP (incl NV centers)

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Introduction:

Favipiravir, a fluorinated pyrazine carboxamide, was used for oral treatment of various RNA virus infections, including Covid-19 and Ebola [1]. We investigated a biocompatible solution of 600  $\mu$ L H2O containing favipiravir (c = 2.124 mM) and riboflavin-5'-monophosphate sodium salt hydrate (c = 0.279 mM) with the goal whether 19F hyperpolarization [2] of favipiravir could be detected using a low-field pre-clinical MRS/MRI setup. The sample was illuminated at 455 nm with a blue high power LED (CREE XP-E, 6mW output). MRS and MRI were performed with a permanent magnet (0.58T, Pure Devices, Wuerzburg, Germany) using a 19F coil for acquiring both 1H and 19F signals [3]. A turbo spin echo sequence served for MRI. At maximum resolution voxel had an in-plane resolution of (0.39 mm)2 and a thickness of 10 mm.

#### Results:

1H MRI served to check the optical fiber position, and 1H MRS for shimming and phase correction of multiple spectra prior to averaging. Both in MRS and MRI a clear hyperpolarization signal could be detected. As the reaction is partly cyclic signal averaging could then be used to increase SNR further. Image-derived information had to be included as the hyperpolarized signal resulted only from a small central part of the volume. Taking this into account when comparing spectra with and without illumination, SE was estimated to be about 1700.

#### Discussion:

The strong hyperpolarization of favipiravir seen at 0.6 T exhibited a higher SE than 3-fluoro-tyrosine [3]. This allowed to detecting even minuscule amounts of the drug using a low-cost pre-clinical MRI/MRS setup and a fully biocompatible model system. Our results confirm the great potential of using photo-CIDNP to combine spectroscopic and imaging studies in biomedical relevant research. Special equipment such as micro-coils may enable to detect even lower amounts of substance similar to recently reported data [4,5], and pave the way to new applications in other biomedical research areas [6].

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**RT 5** 

Optical pumping & SEOP, CIDNP and ONP (incl NV centers)

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Nanodiamonds (NDs) have attracted much attention due, both, to their good biocompatibility and the possibility of hosting, a few nanometers below the diamond surface, stable paramagnetic defect centers with suitable coherence properties. This enables several applications including nanoscale thermometry, quantification of ionic species, magnetic or electric field sensing [1], and also hyperpolarization [2]. In this context, we first discuss original experiments, that rely on optical spin-polarization of the Nitrogen-Vacancy (NV) center, and the application of the PulsePOL sequence [2], to perform hyperpolarization of 13C spins in the diamond lattice. With such protocol, in contrast with reported attempts made using lower magnetic fields [3], we obtain a nuclear magnetic resonance signal for 13C in 100nm particles showing a significant, >170, enhancement over the thermal nuclear signal at 1T. These results constitute a step towards the use of these NDs as tracers for sensitive magnetic resonance imaging. Second, we investigate smaller, 25 nm NDs, targetting abundant g~2 species that have been described as shallow defect centers [4]. We demonstrate the possibility to sense directly via the application of the PulsePOL sequence on these defects, nuclear spins in an external solution. This is illustrated by the detection, besides the signal from 1H terminating the diamond surface [5], of specific resonances attributed to 19F in a fluorinated compound, Fomblin®. Combined with a previous report on the hyperpolarization of external spins using these shallow defects [6], the present experiment gives credit to the idea of using near-surface centers driven with PulsePOL as mediators [7] for transferring polarization from NV centers outside the diamond. We report progress on the implementation of this protocol, which appears more challenging than when the usual in-diamond 13C are involved.

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# HYPERPOLARIZED 13C-ENRICHED PYRUVATES BY SABRE IN ACETONE





## NMR spectra of hyperpolarized pyruvate (top) after 1 scan and thermally polarized (bottom) after 2100 scans.

Signal amplification by reversible exchange (SABRE) [1] can provide strong signal enhancement of different molecules through the creation of a singlet hydride pair with the parahydrogen (pH2) spin isomer, which is a nuclear singlet state. An iridium catalyst may then reversibly bind pH2 derived hydrides and a ligand of interest, allowing polarisation transfer. Among the substrates that can be used as a probe for hyperpolarized NMR and MRI, pyruvate gained much attention. SABRE can hyperpolarise pyruvate in a low cost, fast, and reversible fashion that does not involve the technologically demanding equipment [2]. Most SABRE polarization studies have been done using methanol-d4 as a solvent, which is not suitable for in vivo application [3,4]. The main goal of this work was to obtain hyperpolarized pyruvate in a solvent that is less toxic and with further easy purification steps. For this purpose,

**RT 6** 

acetone-d6 has been chosen. The polarization transfer from parahydrogen to pyruvate was demonstrated at ultralow magnetic fields below 1  $\mu$ T, where the pH2-derived protons and the 13C nucleus of pyruvate become strongly coupled and anticrossings of nuclear spin energy levels occur. The catalyst was activated by bubbling 85% enriched pH2 (Bruker BPHG generator) through the 25 mM pyruvate and 4 equivalents of DMSO-d6 solution for 0.5 h. Then bubbling was performed in the  $\mu$ -metal-shielded solenoid with an internal field of 9 mG for 20s at the room temperature. NMR signals were detected using 1.1T benchtop NMR spectrometer. Upon transfer into a benchtop magnet, hyperpolarised 13C resonances corresponding to free pyruvate at 170 ppm and bounded pyruvate at 164 ppm were observed (Fig.1). Have been reported that at lower temperatures accumulates catalyst-bound pyruvate, which is released into free pyruvate at elevated temperatures [5], this work enables room temperature hyperpolarization of pyruvate in acetone by SABRE. Signals have been acquired after 1 scan, while thermal signals were observed after more than 2000 scans. This work opens new possibilities for obtaining an aqueous solution of pyruvate with further easy purification methods (such as filtration through a C-18 column for catalyst removal and evaporating the solvent).

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### HUMAN SERUM ALBUMIN AS MAGNETIC RESONANCE IMAGING OVERHAUSER DNP SPIN PROBE CARRIER SYSTEM

Liquid DNP, Transport of hyperpolarization

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Ultralow-field (B0 < 10 mT) magnetic resonance imaging (ULF MRI) is driven by the idea of making MRI cheaper and less dangerous to accidents, but it has other strengths as well: Imaging in the vicinity of metals is possible and for some tissue types the contrast is different compared to high field MRI. The poor signal-to-noise ratio at small B0 field strengths is here countered by hyperpolarization using Overhauser Dynamic Nuclear Polarization (ODNP). ODNP transfers spin order from unpaired electrons to nearby protons via an external RF field. At ULF the RF frequency is in the range of 100 MHz, which is a frequency range capable of penetrating large specimen.

As a source for electrons, free radicals can be used. The efficacy of those radicals can be expressed via the parameters Emax (maximum enhancement) and P1/2 (RF power needed to reach half of Emax). For in vivo applications it is important to have as much enhancement as possible at a low RF power level to prevent excessive tissue heating.

For in vivo ODNP experiments, stable and biocompatible free radicals or spin probes are required. Alternatively, efficient, but potentially unstable and toxic spin probes can be embedded in biocompatible carrier systems. Such a carrier system is e.g. human serum albumin (HSA), which we tested within this study for its suitability for future in vivo experiments.

Various nitroxide-modified biocompatible human serum albumin (HSA-NIT)[1] molecules were tested for their ODNP properties. The ODNP effect was used to track the cleavage process of the spin probes from the HSA-NIT, while exposed to the enzyme trypsin. Since the spin probes in HSA-NIT are shielded from surrounding protons, only a weak ODNP effect can be observed. The trypsin cleaves the spin probes from HSA whereupon a strong ODNP effect appears on a time scale of  $\sim$  5 hours. HSA-NIT was shown to have a long shelf life in the intact state.

An Emax of 59.9 and P1/2 = 10.8 W (TEMPO free radicals show Emax = 154 and P1/2 = 6 W in the same setup[2]) were achieved. For PRF = 3.9 W, an enhancement of 20 was obtained.

In a subsequent cell experiment with MCF7 cells, it was shown that the cells did not take up the HSA-NIT in detectable amounts, nor were the cells' proteases able to activate it.

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#### NUCLEAR SPIN ISOMERS OF ETHYLENE: CHEMICAL SYNTHESIS USING PARAHYDROGEN

**RT 8** 

PHIP



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Isomerism is a general phenomenon in chemistry describing the existence of molecules with identical molecular formula, but different structure and properties. However, the existence of molecules in distinct nuclear states is much less common. One of the most widely known example is nuclear spin isomers of dihydrogen molecule – orthohydrogen and parahydrogen. The latter one has gained wide recognition in hyperpolarized NMR. However, while molecular hydrogen can be easily enriched by its cryogenic cooling above a paramagnetic catalyst, this approach does not work for polyatomic molecules. This problem can partially be solved by the chemical synthesis of NSIMs using parahydrogen: it was demonstrated that for acetylene hydrogenation with parahydrogen over heterogeneous catalyst the singlet spin states of two H atoms of the pH2 molecule can persist in ethylene . Unlike the PHIP experiments, this does not lead to the enhanced signals of ethylene because of the magnetic equivalence of its protons. To confirm that NSIM enrichment takes place, ethylene is introduced in the subsequent reaction with the formation of the nonsymmetric product. Here in this work, the reaction with bromine water was used and the polarized signals of 2-bromoethanol (the main product) were analyzed. Three heterogeneous catalysts were used for enrichment of ethylene NSIMs – Pd/TiO2, PdIn/Al2O3, and immobilized [Ir(COD)(L)C1]@SiO2. For all three catalysts the stereospecificity of pH2 addition was found (syn- or anti-) and the method was proposed to assess the stereospecificity of hydrogen addition. The interconversion between NSIMs of ethylene was studied in the gas phase
and the biexponential decay of polarized signals is observed. The equilibration times depend on the stereospecificity of pH2 addition and the type of heterogeneous catalyst used. The effective catalyst is proposed (PdIn/Al2O3); in this case the polarized signals from 2-bromoethanol were observed even after ethylene storage for 1h indicating the presence exceptionally long-lived states. During 30s of storage, isomers are balanced within the same spatial symmetry classes (Ag $\rightleftharpoons$ B3g and B1u $\rightleftharpoons$ B2u). This process corresponds to the short part of the biexponential decay. With further storage (>30s), interconversion between isomers of classes g and u occurs (corresponds to the long part of the biexponential decay). The experimental observations are explained using spectra simulations and analysis of ethylene NSIMs populations.

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# EXPLORING AMPLITUDE MODULATED PULSED DNP EXPERIMENTS USING FOURIER SYNTHESIS

# General theory, Loss of hyperpolarization & relaxation

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# Fourier expansion of the Hamiltonian in Hilbert space is transformed into Floquet space resulting in analytical terms for the magnitude of transition amplitudes between two degenerate states that can be assigned to experimental resonance conditions.

Dynamic Nuclear Polarization (DNP) is a powerful technique to increase the sensitivity of nuclear magnetic resonance (NMR) experiments [1]. Currently mostly continuous-wave (CW) based DNP techniques (e.g., based on solid-effect or cross-effect mechanism) are used where the efficiency of the polarization transfer scales with the inverse of the external magnetic field (B0) [2,3]. Pulsed DNP experiments such as TOP-DNP, XiX-DNP and TPPM-DNP were expected to resolve this issue and were claimed to lead to field-independent DNP transfer [4,5]. However, experimental evidence of a field-independent performance using pulsed DNP schemes is still missing.

To gain further insight into pulsed DNP experiments we describe the time-periodic amplitude modulation of those sequences as a Fourier expansion. We denote this new description of pulsed DNP experiments as Fourier-Synthesized (FS) DNP sequences. In a further step, we use matrix-based Floquet theory [6] to describe FS DNP sequences and to analyze their performance as a function of the static magnetic fields. This approach allows to assign each resonance condition (where enhancement of the nuclear signal can be observed) to particular modes of the Fourier expansion. In addition, it also leads to analytical expressions for the offset frequency on the electron spin for each of the resonance conditions and more importantly for the magnitude of the transition amplitudes. Analysis of those expressions reveals that the efficiency of current pulsed DNP experiments is also B0-field dependent and the efficiency scales similarly to the CW DNP experiments. Therefore, pulsed DNP sequences are only field independent if the amplitude of the microwave irradiation is scaled linearly with B0, which is the same restriction as for CW DNP or NOVEL[7]. We have implemented experiments based on the FS-XiX sequence using OX063 Trityl radical in

glycerol- d8:D2O:H2O (6:3:1 by volume) at X-band (0.35 T) and a temperature of 80 K.

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# OFF-THE-SHELF GD(III) COMPOUNDS AS EFFICIENT HIGH-SPIN METAL ION POLARISING AGENTS FOR MAGIC ANGLE SPINNING DYNAMIC NUCLEAR POLARISATION

**RT 10** 

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# 15N NMR spectrum of [2-13C,15N]-glycine doped with 20 mM Gd(NO3)3 in H2O/D2O/glycerol-d8 (1/3/6 v/v/v) at 105 K and 9.4 T, with and without microwave irradiation at the optimum negative positions of the NMR signal enhancement profiles (inset).

Significant solid-state NMR sensitivity enhancements may be achieved using dynamic nuclear polarisation (DNP),[1] with much of its progress being driven by the rational design of efficient biradical-based polarising

agents.[2] However, these are typically not commercially available, and often require lengthy, expensive, and lowyielding synthesis. Based on previous work using paramagnetic metal ion complexes (such as Gd(DOTA) and Gd(tpatcn)),[3,4,5] we introduced the use of Gd(NO3)3 as an easily accessible and inexpensive "off-the-shelf" polarising agent without the need for chemical synthesis.[6] We have demonstrated that when considering polarisation build-up times and paramagnetic bleaching effects, appreciable sensitivity enhancements for 13C and 15N in [2-13C,15N]-glycine may be achieved at both 9.4 T (-35 for 13C and -197 for 15N) and 14.1 T (-20 and -68). Analysis of the DNP enhancement profiles and electron paramagnetic resonance spectra revealed that the solid effect is the dominant polarisation transfer mechanism. Current work is looking at investigating the impact of the Gd(III) concentration and source to optimise these promising enhancements further, and render the DNP methodology more accessible for the wider NMR community.

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# HYPERPOLARIZED SAMPLES FOR LARGE ANIMAL EXPERIMENTS WITH NEXT-GENERATION POLARIZERS

RT 11

Dissolution/Melt DNP

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As next-generation dissolution DNP (dDNP) polarizers are advancing to higher field strengths and more sites around the world move into large animal and/or clinical studies, there is a need for new formulations of hyperpolarized metabolic contrast agents (HMCA). While methods for producing HMCAs have been documented for lower-field dDNP polarizers [1], we present a selection of substrates optimized for high-field polarization and targeted to brain research in large animals.

Typical doses of HMCA for humans and large animals calls for high molar solid-state concentrations and an efficient dissolution process. Pyruvic acid (PA) has been widely used as the gold standard due to its vitrifying properties as a liquid with high concentration (14M). Other endogenous HMCAs may require the addition of water and co-solutes to achieve vitrifying liquids, resulting in lower concentrations and larger sample volumes relatively to PA, which may pose a problem especially for the large dose sized required in porcine and human experiments.

In this study, we demonstrate how three other metabolic contrast agents – KIC (2-ketoisocaproate), fumarate and alanine – can be polarized at a high field at levels comparable to PA and at concentrations suitable for large animal and human studies. The substrates play key roles in neurochemical balance and neuronal communications, and have sufficiently long T1s for metabolic investigations by spectroscopic imaging.

KIC behaves physiochemically similarly to PA and does not require glassing agents. In its neat form, it has a concentration of 8M. It is particularly suitable for examining the glutamate-glutamine shuttle in neurons and astrocytes which holds significance in various diseases [2].

Fumarate may enable direct examination of metabolic activity in the Krebs cycle, which may change in many diseases or during normal aging [3]. Hyperpolarized [1,4-13C] fumaric acid requires a glassing agent and solvent to be vitrified and solubilized, and thus has lower concentration and a slightly more involved sample preparation.

L-[1-13C] alanine can be polarized by dDNP and is a candidate for probing amino acid metabolism as well as cancer grading [6]. The solubility of alanine can be enhanced when in its basic or acidic salt, and a glassing agent may be required for vitrification [4].

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#### DISTANT DIPOLAR FIELD EFFECTS ON PARAHYDROGEN-INDUCED POLARIZATION

**RT 12** 

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Nuclear spin hyperpolarization provides a promising route to overcome the challenges imposed by the limited sensitivity of NMR spectroscopy. Recently, it was demonstrated that solutions of highly polarized source molecules can be created by dissolution of optically polarized pentacene-doped naphthalene crystals. This in turn enabled a transfer of magnetization to target molecules via intermolecular cross-relaxation and offered an alternative mechanism for the hyperpolarization of external nuclei of the target molecules [1].

In order to make this technique more accessible, we extended our work by using Para-Hydrogen Induced Polarization (PHIP) as a tool to produce highly concentrated and polarized solutions that yield high molar polarization. Molar polarization is then a product of concentration, number of polarized spins within the molecule and spin polarization. The spin polarization is attained by converting parahydrogen-derived singlet order using low-field polarization transfer with Spin-Lock Induced Crossing (SLIC) protocol adapted from highfield NMR [2,3]. We apply this technique on (1-13C,d6)-dimethyl maleate (DMM) which is produced by reacting (1-13C,d6)-dimethyl

acetylenedicarboxylate with para-hydrogen in acetone-d6.

We demonstrate that spin polarization is significantly limited at high quantities of DMM and does not scale proportionally with concentration. We interpret this phenomenon as interference between polarization transfer scheme and a distant dipolar field produced by strongly polarized nuclear spins at high density [4]. Experiments involving strong off-resonant decoupling combined with a modified SLIC protocol illustrate that suppression of demagnetizing field alleviates the limit and successful implementation results in 0.4 mol/L molar 1H polarization in organic solution of (1-13C,d6)-dimethyl maleate. This displays a striking boost to molar polarization over 0.05 mol/L achieved using the unmodified method and opens promising prospects for the further PHIP utilization with new hyperpolarization methodologies.

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# DNP-ENHANCED MAS NMR OF MICRORNA-34A IN HUMAN ARGONAUTE-2 PROTEIN

**RT 13** 

Applications, CIDNP and ONP (incl NV centers), MAS-DNP

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DNP-enhanced MAS NMR of microRNA-34a in hAgo2 protein

Micro-RNAs (miRs) are short 21-22 nucleotide oligo that regulate gene expression by targeting the 3'-Untranslated region (3'UTR) of the mRNA via RNA-induced silencing complex (RISC). They are mis-regulated in various cancer and recently miR-34a was used in a phase-1 clinical trial against terminal liver cancer patients [1]. However, due to high mortality further trials were halted. One of the reasons for this high mortality is the low target specificity of miR-34a with about 100 experimentally proven mRNA targets. Increasing the target specificity can aid in improving the clinical trial results. miR-34a was shown to attain a low populated, high energy excited state when complexed with 3'-UTR of sirtuin-1 (SIRT1) mRNA. Stabilising this excited state led to a twofold increase in SIRT1 repression [2]. Similar ES might be present for other targets and identifying them can aid in development of miR-34a as a cancer therapeutics. However, such information and the exact conformation of miR-34a in RISC is currently missing. In this study, DNP-enhanced MAS NMR is used to characterise the structure of miR-34a within human argonaute2 protein (hAgo2), the crucial part of RISC. Although crystal structures of hAgo2 are present with various guide-RNA, modelling of the nucleotides beyond the seed region is ambiguous due to lack of electron density. Additionally, it was shown that only ~5% of total purified hAgo2 can be loaded with miR-34a [3]. This makes DNP a well-suited technique to study the hAgo2:miR-34a complex when the RNA is isotopically enriched. Excellent signal enhancement of 180 was observed with 2 pmol of miR-34a. This allowed for the acquisition of 13C-13C DARR and 31P-13C TEDOR spectra allowing the study of sugar puckering of miR-34a within hAgo2. This can be used to model the orientation of the nucleobase and backbone within RISC. Correlation to miR-34a from the unlabelled hAgo2 is also observed. Molecular dynamics simulation, BMRB database and experimental observations led to the identification of the amino acids responsible for these correlations. The structural changes of miR-34a in hAgo2 when complexed with SIRT1 target is also reported. The 31P resonances at chemical shifts > 10 and < -6 ppm are

also observed, suggesting a large difference in the charge distribution within hAgo2. It is anticipated that this study will initiate the application of DNP to study the miR regulation by RISC.

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# TOWARDS BIOMEDICAL APPLICATIONS OF PARAHYDROGEN INDUCED POLARIZATION BY SIDE-ARM HYDROGENATION USING SAMBADENA

**RT 14** 

General theory, General Instrumentation, Applications, PHIP, Dissolution/Melt DNP, Liquid DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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Using the singlet spin order of hydrogen, polarization of ethyl acetate in MRI is achieved, and the associated purification for biomedical formulation is presented.

#### Introduction

Parahydrogen-induced polarization (PHIP) through side-arm hydrogenation (-SAH) has enabled the rapid production of aqueous 13C-polarized solutions with a small footprint[1]. Our recent study introduced Synthesis Amid the Magnet Bore, which significantly enhanced nuclear alignment (SAMBADENA) [2]. However, the SAMBADENA hyperpolarization (HP) of PHIP-SAH precursors and production of purified biocompatible solutions have not been demonstrated. In this study, we present a SAMBADENA setup consisting primarily of commercially-available components, capable of generating 300µL of HP ethyl acetate-d6 every two minutes with purification.

#### Methods

Polarization occurs in a standard 5mm NMR tube positioned at the isocenter of a preclinical 7T MRI system. Vinyl acetate-d6, dissolved in acetone, undergoes hydrogenation with para-hydrogen in the magnet bore, followed by RF pulsed polarization transfer using ESOTHERIC [3]. Similarly to a previous report [4], the resulting HP ethyl acetate-d6 is then converted to acetate-d3 by adding an aqueous sodium hydroxide solution and heating it in a water bath at 100°C for 10 seconds. Subsequently, the solution undergoes a 53mbar vacuum for 10 seconds in a 50°C water bath. After removing the acetone, a phosphate-buffered saline solution is added to adjust the solution's pH and isotonicity. Finally, precipitated catalyst is removed by collecting the solution into a syringe through a microporous syringe filter.

#### Results

Using this setup, ethyl acetate-d6 was polarized up to 16%. The cleavage and subsequent purification process yielded up to 88% of the initial amount of vinyl acetate-d6. The traces of acetone-d6 are below the detection limit of the 9.4T NMR, and solutions appear transparent showing no visible leftover of catalyst.

#### Discussion

The observed 13C polarization likely suffer from incomplete hydrogenation, inhomogeneous B0 field, and limited B1 1H excitation bandwidth[5]. The method should also be adapted for isotopically enriched substrates to quantitatively enhance polarization after purification. By applying the cleavage and purification protocol to hyperpolarized samples, initial pilot biomedical applications using SAMBADENA are forseen.

#### Conclusion

While the polarization and agent concentration can likely be improved, they are already adequate for preclinical studies. This technique and setup are accessible to numerous research groups, offering the potential to accelerate the translation of PHIP.

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# IMPROVED POLARIZING AGENTS AND COST-EFFECTIVE SUSTAINABLE CRYOGENIC HELIUM MAS FOR HIGH FIELD DYNAMIC NUCLEAR POLARIZATION

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#### Indomethacin microcrystals impregnated with 10 mM cAsymPol-POK

MAS-DNP has revolutionized the scope of many solid-state NMR experiments by enabling new sensitivity-limited experiments. For instance, we have recently demonstrated DNP-enabled natural abundance 13C-13C and 15N-13C correlation experiments that can be used for crystal structure determination of small molecules 1 and to study disease-relevant protein aggregates 1, as well as 31P-31P correlation experiments to study ligand arrangement at the surface of semiconductor nanocrystals 2. Nevertheless, the returned sensitivity obtained with DNP at low temperature (100 K) is still far from optimal, especially at high magnetic field (> 10 T) and fast MAS (> 20 kHz).

I will first highlight our effort towards developing new polarizing agents guided by MAS-DNP simulations3. The performance of new members of the AsymPol3,4 and of the PyrroTriPol5 families will be discussed highlighting their excellent performance at high field, fast MAS, especially when targeting protonated matrix with short 1H bulk T1n.4-6 In a second part, I will also discuss the Grenoble approach7 to sustainable and cost-effective ultra-low temperature NMR and DNP.8 The approach relies on the use of a closed-loop He cycle to spin and cool the sample, enabling faster sample spinning and significantly improved sensitivity. In recent years, we developed a second-generation He DNP probe with improved thermal capabilities. Impressively, this allows reaching 30 K at the sample while using only a single two-stage cryo-cooler and a single compressor for Bearing/Drive/VT. The sample can be changed in minutes using an innovative cryogenic sample exchange system that prevents moisture to enter the system. Beyond describing the new instrumentation, I will also discuss the huge sensitivity improvement that one can achieve when combined with the latest generation of in house polarizing agents. This will be illustrated on challenging systems (proton-dense methyl-containing organic powdered and CsPbBR3 perovskite NCs) that are difficult to polarize at 100 K because of the short 1H T1n and/or the large microwave absorption.8

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#### DNP PROBEHEAD FOR LIQUIDS AT 9.4 TESLA WITH IMPROVED TEMPERATURE STABILITY

**RT 16** 

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Here we describe the design and performance of a probehead for Overhauser DNP and solid-effect DNP on 1H and 13C in liquid samples with a volume of up to 100 nl. The heat dissipation in the sample has been significantly improved compared to the previous probe design [1], which makes it possible to maintain temperature of the liquid sample almost independent of the applied microwave power up to several watts from a 263 GHz gyrotron [2]. This improved heat dissipation makes it possible to separate the effect of sample temperature and applied microwave power on the efficiency of DNP in liquids at high magnetic fields, and to obtain a quantitative determination of the microwave saturation factor by observing the suppression of paramagnetic shift depending on the applied microwave power [3]. Temperature stability of the probe was tested with ethylene-glycol, and DNP performance was tested in some glycerol samples [4]. Proton decoupling under DNP conditions has been demonstrated on a 13C-labeled aqueous sodium pyruvate solution at ambient temperature [2].

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# CHARACTERIZATION OF MICRO- AND MESOPORES OF ETS-10-BASED TITANOSILICATE CATALYSTS BY HYPERPOLARIZED XE-129 NMR

**RT 17** 

Applications

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In this contribution, the hyperpolarized Xe-129 NMR spectroscopy is used to characterize products of synthesis and post-synthetic treatment of titaniumsilicate catalysts ETS-10 [1]. This catalyst revealed high activity in the conversion of oil with methanol to biodiesel compared to existing zeolite-based materials. The introduction of mesopores by post-synthetic treatment with hydrogen peroxide and a subsequent calcination step results in the generation of an additional active surface with Brønsted basic sites becoming accessible for triolein and enhancing the rate of transesterification reactions. The screening of products prepared under different conditions by Xe-129 NMR including 2D EXSY experiments allowed to identify materials with high interconnectivity between micro- and mesopores. Combined with other characterization methods, including Si-29 magic angle spinning NMR, the obtained results enabled the detailed understanding of the impact of the post-synthetic treatment applied to the ETS-10 titanosilicate with respect to the catalytic activity in the heterogeneously catalyzed reactions [2].



# AN INTRODUCTION TO THE RADIATION DETECTION MRI: THE GAMMA-MRI PROJECT.

**Optical pumping & SEOP** 

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In terms of nuclear magnetic resonance (NMR), modern developments in diagnostic imaging are most commonly aiming toward higher resolutions, via the application of stronger magnetic fields. If possible, like in the exemplary case of 129Xe pulmonary imaging, the signal intensity can be increased with spin-exchange optical pumping (SEOP) hyperpolarization in the gas phase, achieved before the inhalation.

Herein, we would like to present the concept of merging two complementary techniques, namely single-photon emission computerized tomography (SPECT) and magnetic resonance imaging (MRI) into a new modality, called Gamma-MRI. This technique employs isomers of xenon (e.g. 129mXe and 131mXe) as the radiotracers suitable for yielding gamma-ray signals with up to five orders of magnitude higher sensitivity when compared to standard 129Xe NMR (SPECT component), while the spatial resolution remains preserved (MRI component) [1]. In addition, the selection of xenon allows for combining  $\gamma$ -MRI with the classical SEOP hyperpolarization technique, already well-established for medical applications of Xe isotopes. Overall, up to several orders of magnitude increase in signal intensity is expected, coming from only a pM concentration range of the radiotracers. Furthermore, the gamma-ray signal for the image reconstruction can be detected in reasonable acquisition time and at ultra-low magnetic fields (e.g. 0.05 T selected for this project), both being crucial for the feasibility of future medical applications [2].

Contrary to the relatively well-established behavior of 129Xe in biological samples, the NMR properties of the metastable xenon isotopes I131mXe = 11/2 and I133mXe = 11/2, are not yet well understood in both encapsulated and dissolution conditions. Hence, a complementary analysis of the stable quadrupolar xenon nuclei I31Xe (I = 3/2), having comparable natural abundance to 129Xe, should be done to provide general insights into the NMR of quadrupolar xenon isotopes, especially focusing on the magnetic resonance parameters, such as relaxation times and spin-spin exchange rates, in various types of biological solutions, and/or Xe-based biovectors. For this reason, I31Xe solutions containing different types of encapsulating agents (selected based on their capacity to extend nuclear spin relaxation times in 129Xe) are currently being investigated.

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# INNOVATIVE SOLVENT-FREE POLYMER SAMPLE PREPARATION METHODS FOR DNP SSNMR

RT 19

#### MAS-DNP

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Solid-state NMR (SSNMR) is highly suitable for analyzing polymers but lacks sensitivity, which prevents the detailed elucidation of structural features such as polymer chain ends. This limitation can be overcome using dynamic nuclear polarization (DNP), a technique that enhances NMR sensitivity by transferring the electronic spin polarization of polarizing agents to surrounding nuclei [1]. However, among synthetic polymers, mainly soluble ones can be analyzed by DNP SSNMR because efficient methods for preparing the samples for DNP usually require initial polymer solubilization [2]. In this work, we will present two innovative solvent-free sample preparation methods based on the use of supercritical CO2 (scCO2) technology. More precisely, regarding the first method, scCO2 is used as a plasticizing agent to lower the polymer glass transition/melting points, allowing thus an efficient mixing of polarizing agents (PAs) within the resulting soften/molten polymer matrix, similarly to a conventional polymer extrusion process but at moderate temperatures. As a proof of concept, this method was applied to incorporate either TEKPol [3] or AMUPol [4] as polarizing agents within different common soluble polymers. On the other hand, preliminary results related to the use of scCO2 for polymer impregnation will also be presented. For this second method, scCO2 is used as a solvent that can be easily removed by depressurisation. This method allows polymers to be homogeneously loaded with PAs. Different experimental protocols will be presented, allowing PS samples to be impregnated with bTbK (another commonly used PA). The resulting samples were characterized by CW EPR and DNP SSNMR. The results were compared to conventional polymer sample preparation methods (especially Film Casting) highlighting the potential of the proposed processes as new and efficient methods to prepare polymer samples for DNP [5].

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Yao Fu

# ROOM TEMPERATURE OVERHAUSER DYNAMIC NUCLEAR POLARIZATION ON ORGANIC SEMICONDUCTORS

**RT 20** 

General theory, General Instrumentation, Applications, PHIP, Optical pumping & SEOP, CIDNP and ONP (incl NV centers), Triplet DNP, MAS-DNP, Dissolution/Melt DNP, Liquid DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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The overhauser effect (OE) is commonly observed in liquids, metals, and insulating solids. However, its potential in other materials, such as organic semiconductors, has not been fully explored. In this study, we push the boundaries of OE by observing OE effect in organic semiconductors for the first time at room temperature.

Our investigation focuses on a series of neutral open-shell trityl-based di- and poly-radicals. To achieve high spectral resolution, we utilize a super-fast spinning rate of up to 60 kHz, which allows us to obtain individual 1H dynamic nuclear polarization (DNP) enhancement for each sample. Additionally, we employ continuous wave electron paramagnetic resonance spectroscopy (EPR) and pulsed EPR from room temperature to 5 K to characterize the electron spin system.

Our results show that the di-radicals have a localized triplet state, while the poly-radicals are highly delocalized, which may explain their strong OE effect. This finding is supported by the significant DNP enhancement observed in the poly-radicals. Our study provides new insights into the OE mechanism in conductive polymers and suggests that the degree of delocalization of the electron spin system plays a key role in determining the OE efficiency.



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#### ACCELERATION OF 129-XENON RELAXATION FOR PHANTOM MEASUREMENTS UNDER PHYSIOLOGICAL CONDITIONS IN PREPARATION FOR IN-VIVO SEQUENCE OPTIMIZATION OF HYPERCEST AT 9.4 T

RT 21

Applications, Loss of hyperpolarization & relaxation

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Xenon HyperCEST is a novel MRI technique that utilizes hyperpolarized (hp) 129Xe as a contrast agent to detect and image specific molecules or functional groups with high sensitivity and specificity. It operates on the principle of chemical exchange saturation transfer (CEST), in which the exchange of magnetization between free hp xenon and transiently target-bound Xe is exploited to enhance the MR signal of the target molecules. [1]

For its translation to in-vivo animal experiments, it is beneficial to perform meticulous in-vitro sequence testing and saturation optimization to ensure an optimal experimental setup and parameter estimation. To simulate physiological conditions in-vitro, a phantom solution shall be prepared that would serve as a reliable and reproducible test medium for HyperCEST experiments. This includes a reduction of T1 and T2 relaxation times as well as considering the temperature to replicate tissue-like conditions.

In this first study, performed on a Bruker Avance III HD console at 9.4 T, a gas mixture of 2% Xe, 10% N2, and 88% He was injected into a 1 ml sample solution for 15 seconds at a flow rate of 100 ml/min and an operating pressure of 4.5 bar (abs.).

The T2 relaxation times of hp Xe were measured using a conventional CPMG sequence with varying TE, and the influence of different concentrations of BSA (Bovine Serum Albumin), antifoam A, copper sulfate, and gadolinium chloride was investigated. In addition, T1 relaxation times of hp Xe were measured by bubbling hp 129Xe into the phantom and recording the signal after various time delays of up to 45 seconds.

Using a combination of a 6%-BSA solution and an antifoaming agent (Antifoam A) significantly reduced T2 to physiological values of 10-20 ms [2] compared to the tens of seconds in pure water. The BSA-induced foaming was suppressed by the antifoam agent, which also contributes to T2 shortening. Copper sulfate with its paramagnetic ions also reduced T2, but not to physiological values and negatively affected 129Xe signal detection.

To address T1, GdCl3 was used, achieving a decrease from 66 s in pure water [1] to around 6 s at 1 mM, while only slightly affecting T2. Further investigation is needed to understand the combined impact of multiple compounds on hp Xenon's relaxation times.

Developing a solution phantom that mimics tissue properties would provide a reliable and reproducible test medium for HyperCEST experiments and facilitate consistent and controlled investigations, paving the way for more advanced experimental designs.

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**RT 22** 

Applications, Dissolution/Melt DNP, Liquid DNP, Loss of hyperpolarization & relaxation

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#### Cryogenic and dissolution DNP on γ-irradiated and impregnated powder samples

Cryogenic Dynamic Nuclear Polarization (DNP) is an essential step of dissolution DNP (dDNP) [1]. The first step in the dDNP experiment involves placing the solid or liquid sample to be hyperpolarized in a suitable glassing matrix, co-formulated with a paramagnetic source that will be the subject of microwave (mw) irradiation. Unless the analyte to be targeted self-glasses, such addition of a polarizing agent further dilutes –and hence reduces the sensitivity– of the final solution-state NMR measurement. Avenues to circumvent the reduced sensitivity involve induction of radicals via UV-irradiation [2] or via electrical discharge, [3] alleviating issues of introducing a foreign radical or dilution by a "DNP juice". The present study explores the possibility of employing transient radicals formed in situ via  $\gamma$ -irradiation [4] or permanent radicals introduced by soaking a solid with minimal quantities of a suitable wetting solution [5]. The EPR spectra, 1H NMR signals under static DNP conditions, and preliminary results on their dissolution DNP [1] performance monitoring 13C signals of samples obtained by these means, will be discussed.

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# DYNAMICS ON THE SURFACE VIA ELECTRON AND NUCLEAR SPIN PROBES

**RT 23** 

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The study of the dynamics of molecules adsorbed on the surface is crucial for developing modern porous materials widely used in scientific and industrial applications. The information about pore-size distribution, shape and structure of pores, diffusivity, wettability, etc., can be conventionally obtained by using the NMR method via relaxation time distribution and diffusion measurements, NMR spectroscopy, etc. [1]. Furthermore, the scale of dynamics processes probing by NMR can be adjusted via time- or frequency-dependent experiments. The latter can be carried out using fast-field-cycling (FFC) NMR relaxometry [2], which provides relaxation time frequency dependencies, allowing analysis of dynamics in the range of 10-9-10-5 s of corresponding correlation times. Additionally, increasing the selectivity of NMR measurements is achieved by labelling particular surface regions or molecules in the porous systems with an adsorbate. Using electron spins as a label on the surface of porous media provides selectivity via increased NMR relaxivity, while the information about environment of electron spin labels can additionally be studied using EPR techniques. The combination of the two abovementioned approaches reveals dynamic nuclear polarization (DNP) [3] as a great tool to probe dynamics on the surface of porous materials in addition to the increased sensitivity of NMR measurements via hyperpolarization.

In the current contribution, several applications of the DNP method in combination with the NMR FFC technique to study the dynamics of liquid molecules adsorbed on the surface of different porous materials, such as porous silica [4], rocks [5], etc., are discussed. Furthermore, the quantitative analysis of DNP data, in addition to the increased sensitivity via DNP mechanisms, which are defined on the surface as a combination of Overhauser and solid effects, supplements relaxation time dispersions obtained by FFC relaxometry. In order to separate intra- and intermolecular contributions, FFC experiments were performed for both 1H and 2H nuclei of water and alkane as protic and aprotic liquids [6].

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# IN VIVO METABOLIC IMAGING OF [1-13C] PYRUVATE-D3 HYPERPOLARIZED BY REVERSIBLE EXCHANGE WITH PARAHYDROGEN.

**RT 24** 

General theory, General Instrumentation, Applications, PHIP, Optical pumping & SEOP, Dissolution/Melt DNP, Liquid DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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#### Procedure used for sample preparation, purification and animal application.

Introduction: Hyperpolarized (HP) [1-13C]pyruvate MRI has shown promise as a technique for grading and monitoring cancer [1]. However, faster, simpler and low cost hyperpolarization technologies are needed. Parahydrogen-induced polarization (PHIP) techniques have emerged as promising candidates to address this need[2]. We demonstrate a fast (6 min) and cost effective production method of HP [1-13C] pyruvate-d3 in aqueous solution using Signal Amplification By Reversible Exchange (SABRE) and Spin-Lock Induced Crossing (SLIC-SABRE) at  $\mu$ T fields [3], followed by purification and in vivo metabolic MRI in mice [4].

Methods: [1-13C] pyruvate-d3 was polarized in CD3OD utilizing a iridium-based catalyst and a dedicated SLIC-SABRE setup operating at B0=50 $\mu$ T. Purification of the solution was achieved by addition of PBS in D2O, evaporation of methanol ( $\approx$ 100°C,  $\approx$ 5mbar), and subsequent filtering of the solution to remove the precipitated catalyst. The entire purification took around 60s. After injection, metabolic conversion of HP Pyruvate was imaged in four healthy mice either using 13C MRI with a CSI sequence or a metabolite selective bSSFP sequence.

Results: Prior to purification we achieved 13.1±3.2% 13C polarization for pyruvate-d3. Our analysis showed that the injected solutions were sterile, non-toxic, pH neutral and contained 30 mM [1-13C] pyruvate-d3 polarized up to  $\approx 11\%$  ( $\approx 150\mu$ L; residual 250 mM methanol and 20  $\mu$ M catalyst). The injection and imaging procedure was tolerated by all mice. Strong 13C signal of pyruvate was detected in aorta and vena cava. While in the kidney mostly lactate was observed, the liver and gut contained considerable amounts of alanine.

Discussion: While the polarization and concentration of pyruvate and the bolus volume in the purified solution were sufficient for initial in vivo metabolic MRI in mice, we anticipate achieving higher yields. To minimize polarization losses, a faster evaporation and automated sample handling is needed. Increasing the bolus volume can be achieved by employing a larger reactor and utilizing B0 and B1 coils that ensure homogeneity over a larger volume. Additionally, enhancing pyruvate concentration can be accomplished by applying vacuum for an extended period to evaporate water.

Conclusion: These results pose a significant step of making HP MRI available to a wider community by making fast, low-cost, and high-throughput PH-hyperpolarization a viable alternative for metabolic MRI living organisms.

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# NANOMOLAR DETECTION OF BIOSENSORS WITH HYPERPOLARIZED 129XE APPLYING A BENCHTOP SPECTROMETER

RT 25

General theory, General Instrumentation, Applications, Optical pumping & SEOP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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The 129Xe Hyperpolarized-Chemical-Exchange-Saturation-Transfer (Hyper-CEST) [1] approach enables highcontrast and high-sensitivity molecular imaging by exploiting xenon biosensors [2]. HyperCEST facilitates through the indirect measurement of hyperpolarized xenon (hpXe) exchange the ultrasensitive detection of biosensors. The xenon bound to the biosensor resonates at a different frequency than the bulk xenon dissolved in the solution and can be selectively saturated by radiofrequency (RF) irradiation. This saturation is subsequently transferred to bulk xenon when bound xenon and freely dissolved xenon exchange and thus the detected bulk xenon signal becomes attenuated. The attenuation rate depends on the saturation frequency, its duration and the RF power as well as the details of the exchange process.

Here, the focus of this presentation is on the application of HyperCEST for biosensing in vitro utilizing a 1.88 T benchtop spectrometer designed for the routine laboratory. The Hyper-CEST pulse sequence was implemented on the benchtop spectrometer and its performance tested at various conditions of RF-saturation [1, 3]. The experiment was conducted on buffer solutions of the small, xenon-binding molecule cryptophane-A monoacid (CrAma) which is also used in biosensing [4]. We investigated in a dilution series the bulk xenon signal attenuation for RF-saturation applied resonantly to CrAma-bound hpXe in comparison to symmetrically applied off-resonant irradiation. A CrAma concentration down in the nanomolar range could be detected indirectly in this manner.

The presented study used a continuous flow 129Xe polarizer coupled with the 1.88 T commercial benchtop spectrometer for in-line operation, this equipment is presented in detail in [5].

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# TRANSPORTABLE RESERVOIR OF NUCLEAR POLARIZATION TO ENHANCE SOLUTION-STATE NMR SIGNALS

**RT 26** 

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Transportable Reservoir of Nuclear Polarization to enhance Solution-State NMR Signals

There is a fundamental issue with the use of dynamic nuclear polarization (DNP) to enhance nuclear spin polarization: the same polarizing agent (PA) needed for DNP is also responsible for shortening the lifetime of the hyperpolarization. As a result, long-term storage and transport of hyperpolarized samples is severely restricted and the apparatus for DNP is necessarily located near or integrated with the apparatus using the hyperpolarized spins. In this paper, we demonstrate that naphthalene single crystals can serve as a long-lived reservoir of proton polarization that can be exploited to enhance signals in benchtop and high-field NMR of target molecules in solution at a site 300 km away by a factor of several thousands. The naphthalene protons are polarized using short-lived optically excited triplet states of pentacene instead of stable radicals. In the absence of optical excitation, the electron spins remain in a singlet ground state, eliminating the major pathway of nuclear spin-lattice relaxation. The polarization decays with a time constant of about 50 h at 80K and 0.5T or above 800 h at 5K and 20 mT. A module based on a Halbach array yielding a field of 0.75T and a conventional cryogenic dry shipper, operating at liquid nitrogen temperature, allows storage and long distance transport of the polarization to a remote laboratory, where the polarization of the crystal is transferred after dissolution to a target molecule of choice by intermolecular crossrelaxation. The procedure has been executed repeatedly and has proven to be reliable and robust [1].

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# A COMBINED PYRUVATE PROBE OF 2H AND HYPERPOLARIZED 13C FOR METABOLIC BRAIN MR IMAGING

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Brain metabolism plays a vital role in normal neurological function and is associated with various pathological conditions. Hyperpolarized (HP) 13C and deuterium (2H) MRSI have emerged as promising methods for studying brain metabolism.

The most used probe for HP 13C studies is [1-13C] pyruvate; it is currently being translated to humans with ongoing clinical trials. For brain, this includes promising results for monitoring the (aging of) healthy brain [1], CNS tumors [2], and traumatic brain injury [3]. Deuterium is often administered orally using [6,6'-2H2] glucose and has been explored in both healthy subjects and brain tumor patients [4]. However, no literature exists on a combined 2H and HP 13C probe.

In this study, we aim to develop a combined HP 13C and 2H pyruvate probe for imaging brain metabolism. We compare this dual-purpose probe with the established HP 13C pyruvate probe. We investigate the effect of deuteration on polarization level and build-up times, T1 values, and spectral resolution comparing HP [1-13C] pyruvate and HP [1-13C, U-2H3] pyruvate as well as other labeling configurations when feasible. Hyperpolarization is achieved using dDNP with trityl mediated direct carbon polarization on a high field polarizer (SpinAligner, B0=6.7T, T=1.4K). Enzyme setups with LDH and NADH and brain phantoms are employed to mimic pyruvate to lactate conversion and simulate clinical conditions, respectively. NMR spectroscopy (1T SpinSolve, Magritek, T=301K) and a clinical MR scanner (3T Signa Premier, GE Healthcare) are used for data acquisition.

Through this study, we aim to identify potential differences between HP 13C and deuterated HP 13C pyruvate probes in different labeling configurations and select the most suitable probe for in vivo studies. Going forward, it is necessary to look further at in vivo procedures, probe uptake, and the metabolic processes incl. kinetic isotope effects.

Successful implementation of the combined probe may provide insights into (un)healthy brain metabolism, thereby aiding in the development of diagnostics and therapy monitoring for neurodegenerative diseases.

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# POLARIZATION TRANSFER RATES IN ENDOGENOUS METAL IONS DNP

#### MAS-DNP

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# In endogenous metal ions DNP the steady state signal enhancement is independent of the spin diffusion rate

In metal ions based (MI)DNP paramagnetic metal ions are introduced as dopants into inorganic materials serving as endogenous polarizing agents for MAS NMR.[1] Having the polarizing agents as part of the structure enables signal enhancement within the bulk of the material. In contrast, in the more commonly used exogenous MAS DNP formulations using organic radicals, enhancements are mostly limited to nuclei on the surface. In a previous work we have shown that the steady-state enhancements are independent of the nuclear-electron distance, if the paramagnetic dopant is the main source of relaxation.[2] Thus, large and homogeneous enhancements in the bulk can be obtained without the requirement of spin diffusion. This follows from the fact that both the paramagnetic relaxation enhancement (PRE) and the solid effect (SE) DNP efficiency scale linearly with the square of the dipolar coupling, for a single electron-nucleus couple. This simple model, however, does not consider how the presence of spin diffusion could influence the enhancement factors and buildup times.

In this work we analyze the role of spin diffusion in endogenous DNP by combining experiments with simulations. By controlling the relative amount of the two NMR active lithium isotopes, 6Li and 7Li, in Li4Ti5O12, doped with Fe(III) as polarizing agent, we are able to vary the spin diffusion rates. We observe clear evidence of this from the changes in buildup times of both nuclei, by almost one order of magnitude when comparing samples with 7 and 95% 6Li content. Most interestingly, however, the steady-state enhancement remains constant, independent of the isotope content at values of ~150 and ~50 for 6Li and 7Li, respectively.

In addition, we calculate the polarization dynamics in a large spin ensemble consisting of 6Li, 7Li and polarizing agents coupled to each other via three distinct rates: the SE rate, the PRE rate and the spin diffusion rate. I will discuss how these rates are affected by different factors, such as concentration, coupling strength and MAS. In particular, the presence of large anisotropic dipolar couplings to the paramagnetic centers can give rise to enhanced, electron driven, spin diffusion rates. Simulations are in good agreement with experiments and enable to pinpoint for instance the

effect of relaxation sinks and rationalize changes in DNP enhancement as a function of polarization time.

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# RELAXATION AND EXCHANGE OF NUCLEAR HYPERPOLARIZATION AT LOW TEMPERATURE AND FIELD

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Dynamic nuclear polarization can provide samples with near unity nuclear polarization, but a central challenge to its broader application remains the transfer of relevant concentrations of highly polarized nuclear spins into an NMR or MRI magnet. Bullet-DNP addresses this challenge by shooting the hyperpolarized solid and dissolving it only near the point of use. [1,2]

To quantify potential polarization losses during the bullet-transfer at low field for a prototypical DNP sample, we previously reported proton and carbon relaxation [3,4] at low temperature ( $\sim 4 \text{ K}$ ) and field ( $\leq 2 \text{ T}$ ) in pyruvic acid, doped with trityl, using a fast-field-cycling apparatus.

The radical-induced relaxation is found to be sufficiently slow for the bullet-transfer and the results can be described using a thermodynamic model with a minimal set of adjustable parameters, where we calculate triple-spinflip rates from first principles. The analysis indicates that the radical's effect on protons is limited even at low fields due to the electrons' non-Zeeman reservoir's limited heat capacity. Trityl does however couple to both proton and carbon spins, leading to a reduction in the carbon T1. While this proton-carbon coupling can be used for cross-polarization, we also report a new cross-polarization mechanism that we attribute to exchange with hindered rotational states of methyl groups in the solid. We report first results, discuss its effects and potential uses for bullet-DNP.

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# A 14 T / 7 T DNP / EPR SPECTROMETER FOR THE INVESTIGATION OF DYNAMIC NUCLEAR POLARIZATION MECHANISMS

**RT 30** 

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#### 13.8 Tesla DNP (black) and echo-detected EPR (gray) spectra of P1 center in type lb diamond crystal

Dynamic Nuclear Polarization (DNP) is a hyperpolarization technique that rose to prominence in the past two decades due to its ability to address the most pressing issue of NMR spectroscopy – its limited sensitivity. DNP is the most general hyperpolarization approach that allows for orders of magnitude signal enhancements in a wide variety of NMR applications ranging from materials through chemistry to biology.

In the core of DNP lies polarization transfer from intrinsically highly polarized electron spins to nuclear spins of interest. This is a complex quantum mechanical process, which has been the subject of intense research, one clear conclusion of which is that Electron Paramagnetic Resonance (EPR) data is required for the understanding of DNP, and must be collected under conditions as close as possible to those of DNP.[1,2] This is a challenging requirement since high-field instrumentation capable of simultaneous EPR and DNP measurements is commercially unavailable. Several groups have constructed dedicated dual DNP/EPR instruments operating at 3-7 T fields.[3,4] At magnetic fields >7 T only the dynamics of nuclear spins have been studied so far, while electron spin dynamics have been investigated only theoretically using quantum mechanical simulations.[5-6]

To this end, during the past four years, we have been constructing a dual DNP/EPR instrument operating at 14 T / 400 GHz and 7T / 200 GHz. This instrument is tailored for the detailed investigation of DNP mechanisms "from the electron spin perspective" at high fields. It is capable of DNP, EPR and Electron-Electron Double resonance (ELDOR) measurements. The spectrometer uses a solid-state source with 500 and 100 mW power at 200 and 400

GHz respectively. Phase sensitive EPR detection is achieved using a superheterodyne scheme. The special design of the cryostat and static probes allows for operation in 8 - 300 K temperature range and for temperature stabilization upon sample exchange of only 15 min at 10 K using a cryogen-free system. In addition, we have performed the first high-field EPR experiments under MAS which form a foundation for investigation electron spin dynamics in MAS-DNP experiments. In this presentation we present the details of the spectrometer design and demonstrate its performance in DNP, CW and pulsed EPR and ELDOR experiments.

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# 13C IMAGING OF PYRUVATE WITH SABRE-SHEATH AND LIGHT-SABRE AT ULTRA-LOW FIELD

PHIP

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13C images of [1-13C]pyruvate acquired with a LIGHT-SABRE sequence at 119  $\mu$ T.

In recent years, ultralow-field magnetic resonance imaging (ULF MRI) has come close to clinical applications, due to improvements in computer-aided data processing, enhancing image quality, and from novel, task-specific systems using e.g. Superconducting QUantum Interference Devices (SQUIDs) as magnetic field detectors. ULF MRI enables the opportunity for cheap, light-weight imaging, in addition to providing differing tissue contrast to high-field MRI. The ULF regime applies until ~10 mT, which is the optimal field range for various hyperpolarization techniques, such as Overhauser Dynamic Nuclear Polarization (ODNP) and Signal Amplification by Reversible Exchange (SABRE).

In this work, we aimed to enhance the image quality of ULF MRI with the parahydrogen and non-hydrogenative based SABRE technique, which repeatably transfers the spin order of parahydrogen to a substrate via an e.g. iridium based catalyst. To this aim, we have optimized the spin order transfer from parahydrogen to the substrate via field cycling methods and different RF pulse sequences for the hyperpolarization of a bolus.

In particular, we have focused on polarization of [1-13C]pyruvate. Comparable 13C polarization to SABRE in Shield Enables Alignment Transfer to Heteronuclei (SABRE-SHEATH) with magnetic field cycling was achieved with Low-Irradiation Generation of High Tesla (LIGHT)-SABRE at a constant 119  $\mu$ T magnetic field. LIGHT-SABRE uses a continuous wave spin locking pulse with amplitudes as low as 1  $\mu$ T at a frequency of 1270 Hz, during the hyperpolarization period. As aforementioned, this scheme does not require any magnetic field cycling. This spin locking pulse mimics the SABRE-SHEATH condition, enabling a strong coupling between the hydrogen and the 13C nuclei, within the Ir-complex.

With these hyperpolarization techniques, we have been able to attain enough signal to perform the first hyperpolarized 13C ULF MRI experiments, using [1-13C]pyruvate. Previously, only proton images have been

possible to acquire in the ULF regime. However, employing the two hyperpolarization techniques (SABRE-SHEATH and LIGHT-SABRE) with Spin-Echo (SE) sequences, has made three-dimensional 13C and 1H images in the sub-millimeter voxel size range possible. For the future, we are working on a balanced Steady State Free Precession (bSSFP) sequence to accelerate the overall acquisition time by an order of magnitude This will enable fast, steady state in vivo imaging sequences, which may open up the possibility of tracking a hyperpolarized bolus in real time at ULF.

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# REALISATION OF A RB-XE COMAGNETOMETER FOR NOBLE-GAS SPIN QUANTUM MEMORIES

Optical pumping & SEOP, Transport of hyperpolarization

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Nuclear spin-half systems, made of noble gases (like 3He or 129Xe), show hour-long coherence times in magnetically shielded environments [1]. The polarisation, manipulation and read-out of the long-lived nuclear spin state can be efficiently done via the coupling to the electron spins of alkali vapour atoms. Such vapour-cell based electron-nuclear spin comagnetometers are commonly used in precision measurement [2]. Recently, Firstenberg et al. extended the application to quantum communication and proposed a quantum memory scheme, which should substantially extend the storage time from the millisecond regime achieved in alkali vapour [3,4] into the minute, or even hour regime [5] allowing for the application as a quantum token. In their proposal, the coherent mapping of the photonic spin states onto the long-lived nuclear spins is realised via enhanced intermediation of alkali spins.

Here we present the first steps towards an experimental realisation of the proposed quantum memory. A glass cell containing an Rb-129Xe mixture is placed in a table-top magnetic shield and heated to 80 °C to increase the vapour density. We implemented a dual-axis optical system to characterise the Rb-129Xe comagnetometer. A circularly polarized 795 nm beam optically pumps Rb spins, which gradually polarise 129Xe nuclear spins by spin-exchange optical pumping. A linearly polarized 780 nm beam monitors the polarisation of the Rb spins using Faraday rotation.

The measured parameters are the gas pressure, build-up time of 129Xe polarisation, T2 as well as T1 relaxation times of Rb. We propose a method to measure the coupling rate of 129Xe and Rb, which is crucial for the proposed quantum memory. We manufactured a batch of cells with varied 129Xe pressure to study the impact of gas pressures on the coupling and decay rates. Furthermore, we will present the strong dependence of the coupling rate on the background magnetic field as well as the coherent control of the nuclear spins via driven Rabi nutation demonstrating the long coherence time. The presented calibration of Rb-129Xe comagnetometers provide manifold information on the system, which will be utilised later for the optimisation of experimental parameters. As presented in this work, the coupling rate and the controlled nuclear spin rotation pave the way for a realization of nuclear spin-based quantum memory.

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#### PHOTO-CIDNP MAS NMR STUDY OF ELECTRONIC STRUCTURE AND LOCAL MOBILITY OF CHLOROPHYLL COFACTORS IN A HELIOBACTERIAL REACTION CENTER

**RT 33** 

General theory, General Instrumentation, Applications

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The energy conversion in natural photosynthetic organisms occurs in the heart of the reaction center (RC) complex through an optimized electron transfer with an optimized process with a high quantum yield. The RC complex contains light-harvesting antenna systems, where the light energy is collected and transferred to the RC driving charge separation. A detailed understanding of the origin and evolution of photosynthetic RCs in the structural, kinetic, and dynamical aspects would be a cornerstone to boost the research in the fields of synthetic biology and bio-engineering. The efficiency of the electron transfer might be tuned by the electronic structure and dynamics of cofactors in the charge separation as well as the environment of the protein matrix.

The solid-state photo-CIDNP effect [1,2] is related to this electron transfer event leading to the formation of spincorrelated radical pairs (SCRPs) [3,4] producing non-Boltzmann nuclear spin hyperpolarization. It can be detected in solid-state NMR experiments with a highly enhanced signal originating from electron donor and acceptor cofactors. The effect might be an intrinsic property of electron transfer in all-natural photosynthetic RCs [5].

In the history of Earth, the origin of photosynthetic organisms was anoxygenic and it is suggested that all existing RCs of photosynthetic organisms such as photosynthetic bacteria, algae, and plants evolved from the same common ancestor [6,7]. The heliobacterial RC is supposed to be an evolutionary the most ancient reaction center in the evolutionary scheme since they are simplest homodimeric and loosely bound quinone [8,9].

We investigated the electronic structure and local dynamics over the time scale of milliseconds to nanoseconds of the cofactors including electron donor and acceptor along the electron transfer path via various solid-state NMR experiments taking advantage of the solid-state photo-CIDNP effect and quantum chemical calculations based on density functional theory.

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# 77SE SABRE POLARIZATION VIA SCALAR NETWORK COUPLING IN ZULF

**RT 34** 

*General Instrumentation, Applications, PHIP, CIDNP and ONP (incl NV centers), Triplet DNP, Dissolution/Melt DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation* 

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Single scan 76.4 MHz 77Se NMR spectrum enhanced by SABRE at 0.3 microTesla.

SABRE (Signal Amplification by Reversible Exchange) hyperpolarization has emerged as a powerful technique in the field of NMR spectroscopy, enabling the enhancement of signals by several orders of magnitude. While SABRE has been extensively studied for hyperpolarizing proton, 15N and 13C nuclei, its application to other nuclei, such as selenium (Se), remains unexplored. Selenium is an important element in various biological and chemical processes, and its NMR properties provide valuable insights into molecular structure, dynamics, and interactions. The SABRE technique offers a promising solution to overcome these challenges by harnessing the reversible exchange between para-hydrogen molecules and target molecules containing selenium. to our knowledge, no cases of selenium nuclei polarization by SABRE have been published to date. The low natural abundance (7.6%) and inherently low sensitivity of selenium-77 NMR have posed challenges in its characterization. We report the first detection of 77Se hyperpolarization by SABRE at natural abundance in small molecule of 3methyl[1,2,4]selenadiazolo[4,5-a]pyridine-4-ium chloride (SDAP) in methanol-d4. The conditions for polarization transfer to selenium nucleus spins are optimal in ultralow fields in the range 0.2 to 4 microtesla. The molecule is coordinated in the metal complex by the nitrogen atom N2. Depending on the isotope in the N2 position, we identified two pathways of polarization transfer to selenium in the IrImes complex: for isotope 14N, the polarization is transferred in the coupled three-spin system (77Se-H-H), and for isotope 15N, in the coupled four-spin system (77Se-15N-H-H), the latter was most effective for polarizing 77Se, with an enhancement of 1100 compared to the thermal signal at magnetic field of 9.4 Tesla. 77Se SABRE spectra were measured at various temperatures from 0 to 25 oC. It turned out that for direct transfer in the three-spin system (complex with 14N) the optimal temperature was near 0 oC, and for transfer in the four-spin system with 15N as a mediator the optimal temperature was 25 oC.

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#### SABRE HYPERPOLARIZED 13C PYRUVATE-D3 VIA SPIN-LOCK INDUCED CROSSING (SLIC) AT LOW-FIELDS ENABLES IN VIVO METABOLIC IMAGING

RT 35

Applications, PHIP, Other hyperpolarization methods

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#### Comparisson of hyperpolarized 13C NMR spectra of pyruvate-d3 using SLIC-SABRE and SABRE-SHEATH. Both free (1) and catalyst bound (2) pyruvate species are observable. The inset shows the 13C NMR spectrum of a methanol reference sample.

Hyperpolarized 13C pyruvate is a rapidly evolving tool for assessing metabolic changes in vivo. However, widespread adoption is hindered by the technical complexity of nuclear spin hyperpolarization techniques. Recently,

Signal Amplification by Reversible Exchange (SABRE) hyperpolarization of pyruvate was demonstrated [1, 2], opening up the possibility of a cost-effective, high-throughput polarization modality for pyruvate. In this work, we use Spin-Lock Induced Crossing (SLIC) at 50  $\mu$ T to efficiently hyperpolarize the 1-13C and 2-13C isotopomers of pyruvate [3] and compare this to hyperpolarization using ultra-low (400 nT) fields commonly known as SABRE-SHEATH [4].

For non deuterium labeled [1-13C]- and [2-13C] pyruvate-h3, we observe similar 13C-polarization levels using SLIC-SABRE and SABRE-SHEATH: approximately 10% for C1 and approximately 2% for C2. However, SLIC-SABRE is dramatically more efficient for the hyperpolarization of pyruvate-d3: polarization increased from approximately 4% to 20% for C1 and from approximately 0.2% to 6% for C2. We posit that this is because the rapidly-relaxing deuterium nuclei are not strongly coupled to the polarized 13C spins under SLIC conditions at 50  $\mu$ T. This advance is important not only for the remarkable polarization levels achieved but also because pyruvate-d3 features longer hyperpolarization lifetimes (T1 = 223 ± 16 s at 1.88 T), which translates to reduced polarization losses during purification and quality assurance of the contrast agent.

To demonstrate these benefits, we imaged the in vivo metabolism of SABRE-polarized pyruvate-d3 purified through organic solvent evaporation. In these experiments, we observed downstream metabolites of pyruvate (lactate, alanine) in healthy mice.

We expect that SLIC-SABRE at  $\mu$ T fields can be applied to other deuterium-labeled SABRE-active compounds to enhance polarization.

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#### PARAHYDROGEN-INDUCED HYPERPOLARIZATION FOR FUNDAMENTAL RESEARCH AND PRACTICAL APPLICATIONS

**RT 36** 

Applications, PHIP, Dissolution/Melt DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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Parahydrogen for advanced magnetic resonance applications and novel hyperpolarization approaches

Parahydrogen is a powerful source of nuclear spin hyperpolarization for boosting sensitivity in numerous applications of NMR and MRI. A range of parahydrogen-based techniques are used today to achieve this goal. Parahydrogen can be applied to study the mechanisms of important catalytic processes that involve H2 as a reactant, such as hydrogenation of unsaturated hydrocarbons and related reactions. Remarkably, observation of PHIP in hydrogenation of properly chosen substrates can reveal information on the extent of S-T0 mixing in the reaction intermediates. The latter is found to depend significantly on the nature of the catalyst employed, both for homogeneous and heterogeneous catalytic hydrogenations. Furthermore, PHIP effects can probe stereoselectivity with respect to syn and anti addition of H2 to alkynes upon their selective hydrogenation to alkenes. However, ALTADENA-type experiments may be misleading in this respect, and are sometimes misinterpreted in the literature. Of particular fundamental and practical interest is the hydrogenation of the triple carbon-carbon bond of acetylene. The presence of 13C isotope at natural abundance in the reaction product ethylene lifts molecular symmetry sufficiently to reveal hyperpolarization. Furthermore, while the main isotopologue of ethylene does not exhibit any parahydrogen-derived NMR signal enhancement because of its high degree of symmetry, its chemical production from acetylene and parahydrogen leads to a non-equilibrium ratio of its four nuclear spin isomers. This fact can be revealed by breaking the symmetry of the ethylene molecule in a subsequent chemical transformation. The enhanced NMR spectra produced this way can be used to determine the kinetics of ethylene nuclear spin isomer interconversion, and even to characterize the relative quantities of the nuclear spin isomers produced. The results demonstrate, in particular, that the ratio of different spin isomers of ethylene depends significantly on the type of the catalyst used in the reaction. A facile access to spin isomers of molecules other than H2 and D2 is a major resource for developing novel hyperpolarization schemes. It is remarkable that even metal-nanoparticle-based heterogeneous catalysts can deliver the two H atoms in a correlated nuclear spin state to a hydrogenation product despite the nonpairwise nature of the accepted reaction mechanism. Another notable direction in PHIP research is the production of catalyst-free hyperpolarized substances potentially applicable for biomedical studies, exemplified by some key metabolites and gases.

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### ADVANTAGES OF PHOTO-SABRE: LONG LIVED HYPERPOLARIZATION OF TRANS 15N2-AZOBENZENE IS FORMED BY COMBINING SABRE OF CIS-ISOMER WITH IN SITU PHOTOISOMERIZATION IN ZULF

**RT 37** 

PHIP

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Over the past decade, azobenzene-based molecular photoswitches have emerged as promising control devices in a range of fields, including chemistry, biology, materials science, physics, energy storage and pharmacology. Previous studies revealed that cis isomer of azobenzene gains strong nonequilibrium polarization of 15N nuclear spins through interaction with parahydrogen molecules in the reversible exchange with Ir-complex.1 This technique, known as SABRE (Signal Amplification by Reversible Exchange), enhances inherently weak NMR signals by several orders of magnitude at relatively low operational cost. We demonstrate that performing SABRE in the presence of light irradiation allows to hyperpolarize trans-azobenzene, which direct coordination with the SABRE Ir-complex is sterically hindered.

The proposed approach, which we called photo-SABRE, is robust and efficient, as well as non-destructive and reproducible.2 It combines coherent polarization transfer from pH2 to cis-azobenzene at ultralow magnetic field with the reversible cis-trans-photoisomerization, which results in substantial polarization levels of 1H, 13C, and 15N nuclear spins in both cis and trans forms of azobenzene. Moreover, using photo-SABRE, it is possible to hyperpolarize the long-lived spin order of 15N spin pair in trans-15N2-azobenzene, with a lifetime of about 25 minutes, which greatly exceeds the ordinary relaxation times T1 of its 15N nuclei at high (around 10 s) and low (around 200 s) magnetic fields. This long-lived spin order can also be accessed through the ortho protons of azobenzene, enabling its observation without the need for heteronuclear NMR detection. Photo-SABRE amplification of the NMR signals of cis-trans photoswitchable compounds has a potential to become a valuable tool in the ascending field of photopharmacology and novel light-controlled materials.

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### NANOSTRUCTURE ANALYSIS OF COMPOSITE MATERIALS AND MULTI-LAYER FILMS BY SPIN-CONTRAST-VARIATION NEUTRON SCATTERING AND REFLECTIVITY

**RT 38** 

Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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our DNP apparatus in neutron beamline

The coherent scattering length of polarized neutron against hydrogen, bH, varies greatly as a function of proton polarization PH against neutron spin direction, bH = -3.74 + 14.56PH (fm). Thus, the scattering of polarized neutrons changes with PH accordingly. Spin-contrast-variation (SCV) is a technique of structure analysis from the scattering of polarized neutrons that changes with PH of the sample. SCV was developed in 1989 [1] but referred as non-practical at that time due to difficulty of hyperpolarization. However, development of compact dynamic nuclear polarization (DNP) apparatus by Paul Scherrer Institute [2] opened the door of SCV for practical uses. We introduced the technique, and carry out the SCV small-angle neutron scattering (SANS) [3], neutron reflectivity (NR) [4], and neutron powder diffraction (NPD) [5] studies at Japan research reactor (JRR-3) and Japan Proton Accelerator Complex (J-PARC).

Recently, we analyzed structure of nano-ice crystals generated in rapidly frozen water containing cryoprotective agents of glucose by using SCV-SANS. Whereas the scattering from nano-ice crystals has been hidden in strong scattering from amorphous ice in conventional experiments, our SCV-SANS experiments distinguished between these scatterings. The analysis revealed that the nano-ice crystals generated in a rapidly frozen glucose-dissolved water form a planar structure with a thickness of approximately 1 nm, which is close to the critical radius of ice-crystal nucleation in supercooled water. This result suggests that the glucose molecules are adsorbed on a specific plane of the nucleated nano-ice crystals to obstruct the crystal growth in the direction.

We developed SCV-NR to determine structure of hidden interface in multilayer films [4]. Whereas NR has been used for structure analysis of the hidden interface due to high transmission of neutrons, it has been difficult to distinguish between the neutrons reflected from multiple surface and interfaces. In contrast, SCV-NR distinguishes them from the polarized NR curve that changes with PH. We recently succeeded in observing a nm-thick silane coupling agent (SCA) layer formed by annealing of a rubber-SCA mixture film on silica, and analyzed the entanglement between the rubber and SCA at their interface.

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#### STABILIZATION OF A FLAVOPROTEIN FOR SOLID-STATE PHOTO-CIDNP MAS NMR AT ROOM TEMPERATURE BY EMBEDDING IN A GLASSY SUGAR MATRIX

RT 39

CIDNP and ONP (incl NV centers)

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#### Embedding of flavoproteins into trehalose matrix leads to absorptive photo-CIDNP enhancement

Hyperpolarization via the solid-state photochemically induced dynamic nuclear polarization (photo-CIDNP) effect can be detected in frozen solutions of electron transfer proteins generating a radical-pair upon illumination. The effect has been observed in various natural photosynthetic reaction centers and in light-oxygen-voltage (LOV) sensing domains incorporating a flavin mononucleotide (FMN) as chromophore. [1,2] In LOV domains, where a highly conserved cysteine is mutated to a flavin to interrupt its natural photochemistry, a radical-pair is generated by electron transfer from a nearby tryptophan to the photoexcited triplet state of FMN. During the photocycle, both the LOV domain and the chromophore are photochemically degraded, e.g., by the formation of singlet oxygen. This limits the time for collection of hyperpolarized nuclear magnetic resonance (NMR) data.

We show that embedding of the protein into a trehalose sugar glass matrix stabilizes the protein for 13C solid-state photo-CIDNP NMR experiments which can be conducted at room temperature in a powder sample. Additionally, this preparation allows for incorporation of high amounts of protein further boosting the intensity of the detected signals from FMN and tryptophan at natural abundance. Signal assignment is aided by quantum chemical calculations of absolute shieldings. The underlying mechanism for the surprising absorption-only signal pattern is not yet understood. Comparison to calculated isotropic hyperfine couplings imply that the enhancement is not due to the classical radical-pair mechanism (RPM). Analysis of the anisotropic hyperfine couplings associated with solid-state photo-CIDNP mechanisms also show no simple correlation, suggesting a more complex underlying mechanism.

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### HIGH-FIELD SOLID-EFFECT DNP IN VISCOUS LIQUIDS USING NARROW EPR LINE POLARIZING AGENTS

**RT 40** 

Liquid DNP

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# <sup>1</sup>H DNP field profile and NMR spectrum enhanced by solid effect for tripeptide in glycerol using triarylmethyl radical as polarizing agent at a magnetic field of 9.4 T and 315 K

Dynamic nuclear polarization (DNP) is a hyperpolarization method that is widely used for increasing the sensitivity of nuclear magnetic resonance (NMR) experiments. DNP is efficient in solid-state and liquid-state NMR but its implementation in the intermediate state, namely viscous media, is still less explored. We recently demonstrated that  $\alpha,\gamma$ -bisdiphenylen- $\beta$ -phenylallyl (BDPA) radicals can be used to polarize lipid bilayers in the fluid-phase through the solid-effect mechanism at high magnetic fields [1]. Here, we show that 'H DNP enhancement of over 50 can be obtained in viscous liquids at a magnetic field of 9.4 T and a temperature of 315 K. This was accomplished by using narrow EPR line polarizing agents in glycerol, both a water-soluble BDPA and triarylmethyl radicals, and a microwave/RF double-resonance probehead. We observed DNP enhancements with a field profile indicative of the solid effect and investigated the influence of microwave power, temperature and concentration on the 'H NMR results. To demonstrate potential applications of this new DNP approach for chemistry and biology, we recorded hyperpolarized 'H NMR spectra of tripeptides in glycerol-ds [2]. Moreover, we expanded the applicability of DNP to other nuclei in viscous media, for example <sup>13</sup>C. To hyperpolarize <sup>13</sup>C nuclei we implemented the steady-state solid-effect 'H DNP with subsequent transfer of the 'H polarization to <sup>13</sup>C via INEPT.

This work was supported by the Deutsche Forschungsgemeinschaft (DFG, grant 518679424).

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#### LIQUID-STATE 13C OVERHAUSER DYNAMIC NUCLEAR POLARIZATION AT 9.4 TESLA

**RT 41** 

Liquid DNP

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In recent years, liquid-state Overhauser dynamic nuclear polarization (ODNP) has gained new attention, because it was demonstrated that under microwave (mw) irradiation electron spin polarization can be efficiently transferred to 13C nuclei, reaching signal enhancements of up to 600 at 9.4 Tesla [1,2]. Further mechanistical studies extended our knowledge on the spin polarization mechanism, explaining the experimental observations at high magnetic field [3-6]. Even though some mechanistic hurdles were mastered, several challenges for a broader application of ODNP remain, such as the strong sample heating due to the microwave (mw) absorption of the solvent, line broadening effects, and non-uniform hyperpolarization.

In an effort to combine the significant signal enhancements accessible through ODNP with routine NMR experiments and limit mw induced sample heating, we designed a new DNP spectrometer. It operates at 9.4 T, room temperature, and combines a tunable high-power continuous wave gyrotron with large microliter sample volume.

As our new setup allows for the screening of a large amount of target molecules under a variety of experimental conditions (e.g. variation of solvents, polarizing agents, mw power, irradiation time, and temperature), we were able to identify favorable chemical environments for large 13C signal enhancements at 9.4 T. Signal enhancements of one order of magnitude and above were observed on suitable target molecules under signal averaging conditions.

Finally, we illustrate the feasibility of ODNP in 2D NMR experiments such as 13C-13C total correlation spectroscopy (TOCSY) and Incredibly Natural Abundance Double Quantum Transfer Experiment (INADEQUATE).

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#### PROBING MINORITY COMPONENTS IN MICROPLASTIC VIA MAS-DNP NMR SPECTROSCOPY

**RT 42** 

General theory, General Instrumentation, Applications, Triplet DNP, MAS-DNP

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#### Schematic representation of film casting procedure.

While advantageous material properties make plastic indispensable in our everyday lives, accumulation of mismanaged plastic waste in the environment poses inestimable ecological risks. For better risk assessment of microplastic (MP) several open questions including polymer degradation rates and the degradation and leaching behaviour of incorporated additives need to be addressed. What these challenging questions have in common is the necessity for quantitative analytical tools with low detection limits as minority species are in the focus of interest. Previously, it was shown that conventional NMR spectroscopy is well suited to monitor polymer defects introduced by photooxidation.[1-3] However, analysis is quite time-consuming with a detection limit of roughly 1%. This limits the application to selected samples which are preferentially 13C enriched. To overcome this lack of sensitivity, we apply dynamic nuclear polarisation (DNP). To make microplastic samples DNP active, stable radicals need to be homogeneously distributed in the sample.

Thus, prerequisite is identifying optimal sample preparation methods for the weathered MP samples. This is challenging due to the continuous change of surface compositions and degree of hydrophobicity over the course of weathering. For PS particles as model systems, different methods such as incipient wetness impregnation, glass forming, extrusion and film casting were studied in depth. The evaluation showed that film casting with AsymPol is the best option leading to solvent-free 13C DNP-enhanced NMR spectra with reasonable enhancements. The studies were extended to weathered LDPE and PP MP samples by adapting solvents and processing conditions demonstrating the broad applicability of film casting as versatile preparation technique. Due to the interplay of enhancement and short build-up times the measurement times could be decreased by up to two orders of magnitude. Thus, we were

able to probe polymer defects introduced by weathering much faster and with a significantly lower detection limit. This furthermore allows to characterize the degradation and leaching of polymer additives which are usually added in small proportions.

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### PORTABLE HYPERPOLARIZED XE-129 APPARATUS WITH LONG-TIME STABLE POLARISATION

**RT 43** 

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Xe-129 NMR spectroscopy is an excellent method in life and materials science. The inertness of xenon enables magnetic resonance imaging of living tissue and allows the investigation of guest-host interactions inside liquids and solids without affecting the host. It makes highly sensitive cryptophane-based biosensors possible and is used in protein research to characterise natural soils and porous materials. With a wide chemical shift range, it not only elucidates pore size distribution in the nanometer range but also gives information about the pore geometry.[1]

The low sensitivity of this method leads to long acquisition times. This can be countered by hyperpolarising xenon gas with spin-exchange optical pumping (SEOP), increasing Xe-129 nuclear spin polarisation by four to five orders in magnitude.

We developed an apparatus that can produce a continuous flow of 70 mL hyperpolarised xenon per hour at moderate system pressure.[2] It features a presaturation rubidium cell with a temperature control separated from the oven containing the large vertically positioned two-bodied pumping cell. With recent further improvements, we now reach a polarisation value of 40 % in the pump cell and 20 % at the sample. Consequently, measurements with HP 129Xe take only a fraction of the time and make materials with a small specific surface area accessible for investigation. The long-time stable polarisation is advantageous for time-evolved 2D exchange spectra of adsorbed Xe-129.

We use the highly stable stream of hyperpolarised Xe-129 gas to analyse aged polystyrene microplastic particles with a small specific surface area of only a few square meters per gram. The gained sensitivity through hyperpolarisation renders it possible to see the transition of macroporous voids into microporosities over the ageing time of 3200 h. The quantitative nature of the apparatus will be shown with a time-evolved 2D exchange spectra of xenon absorbed in a metal-organic framework.

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### AUTOMATED BULLET-DYNAMIC NUCLEAR POLARIZATION

**RT 44** 

General Instrumentation, Applications

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Bullet-DNP [1] is a form of dissolution-dynamic nuclear polarization. In bullet-DNP the hyperpolarized target material and a suitable radical are dissolved in a glass-forming solvent, and the solvent is placed into a bullet. The sample is then hyperpolarized under standard D-DNP conditions and then ejected from the polarizer into an injection device for detection in solution NMR magnet. For many years, DNP experiments have been performed without sufficient attention to automating the whole process. Automating this not only eliminates possible human errors during sample preparation and placing it inside the DNP, but also increases the accuracy, efficiency and throughput of the experiments and enables remote experiments over nights or over weekends. In addition, due to the automation of the process, it is possible to perform the experiments can be carried out repeatedly without the need to remove the injection device from the NMR magnet [2]. The instrument presented in Ref [2] still needed manual intervention between experiments.

Here we provide automation solutions for the bullet-DNP. The new fully automated system includes sample selection through a 96 wells microtiter plate, sample injection into the bullet, freezing at -180 °C, automatic loading of the bullet into the DNP insert, shooting from the DNP insert into the injector device for liquid state NMR, and at the end ejection of the used bullet and preparation of the system for the next experiment. The system is still under final development, but will facilitate unsupervised DNP experiments in the near future.

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### HYPERPOLARIZED 129XE NMR TO PROBE TRANSMEMBRANE RECEPTOR-LIGAND INTERACTION

**RT 45** 

Optical pumping & SEOP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation

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Hyperpolarized 129Xe is maturing as a contrast agent in clinical MRI as demonstrated by the recent FDA approval for evaluations of lung ventilation and in ongoing efforts towards the sensing of molecular biomarkers [1]. The developments are based on the favorable properties of 129Xe like the nuclear spin <sup>1</sup>/<sub>2</sub>, the high sensitivity of chemical shift to the molecular environment, the substantial solubility in water and more in lipids, and a detection sensitivity boosted by orders of magnitude through spin-exchange optical pumping. These assets, however, may allow the extension of xenon NMR in vitro towards probing protein dynamics. For example, the important class of transmembrane G protein-coupled receptors (GPCR), expected to populate a conformational ensemble which is modulated by extracellular and intracellular ligands for regulation of essential functions in the human body, are difficult to study by conventional NMR. The obstacles of rather large amounts of material required due to low sensitivity, and fast relaxation, signal overlap or a vast background of natural abundant 13C and 15N because of the massive receptor molecule, may be avoided when using a non-native label, possibly ultra-sensitive and highly dispersive, for background-free measurements. Thus, the feasibility to study GPCR functional dynamics by xenon NMR is investigated using the human neuropeptide Y2 receptor (Y2R). Y2R is involved in various physiological processes, including food intake, neuroprotection and circadian rhythm [2]. The xenon-trapping cage molecule cryptophane-A is attached through a linear linker to an introduced cysteine at a mobile extracellular loop of Y2R, close to the ligand binding site to facilitate chemical exchange saturation transfer experiments for dynamics monitoring. High quality spectra indicative of multiple conformational states of the receptor-cage conjugate are obtained with differences in the number and position of signals depending on the absence or presence of the native ligand neuropeptide Y. Molecular dynamics simulation are employed to assign the spectroscopic signals to contacts of the cage to receptor sites depending on the structural state of Y2R. Overall, a preferred interaction of the xenontrapping cage with the bound ligand over contacts to the protein surface is found. The approach is highly versatile in the freedom to position the xenon label on the receptor, to vary the linker geometry and to expose the receptor to any ligands, thus furthering comprehensive analysis of GPCR conformational dynamics.

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#### OVER 20% 13C-HYPERPOLARIZATION AND FAST IMAGING OF ETHYL-[1-13C]-ACETATE-D6 AND ETHYL-[1-13C]-PYRUVATE-D6 USING SAMBADENA

**RT 46** 

PHIP, Transport of hyperpolarization, Other hyperpolarization methods

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# Fig.-1: 13C NMR of a thermally-polarized reference solution and hyperpolarized acetate and pyruvate precursors (a) and 13C MRI of hyperpolarized [1-13C]pyruvate superimposed with a $\mu$ CT image of the SAMBADENA reactor (b).

Introduction: Magnetic Resonance Imaging (MRI) is one of the most common tools for medical diagnosis. The hyperpolarization (HP) of nuclear spins stimulates enhancing the MR signal by orders of magnitude enabling new MRI applications. Dissolution dynamic nuclear alignment (dDNP) is today's HP standard, but it can cost up to  $\notin$ 3M and takes about an hour to produce an HP contrast agent, while Parahydrogen- (pH2) induced polarization and Synthesis Amid the Magnet Bore Allows Dramatically Enhanced Nuclear Alignment (SAMBADENA) can cost up to  $\notin$ 10K and produces HP agents in seconds.

Methods: Our SAMBADENA setup comprised an actively heated reactor for fast pH2 addition at up to p=32 bar and T=90 °C, a fluid control unit, and the 7T preclinical MRI setup with 1H-13C volume coil. The gas supply and fluids shuttling are controlled by a set of valves, which were operated from the MRI pulse program. For spin order transfer (SOT) the ESOTHERIC sequence was used with two composite refocusing pulses per interval (90°x-180°y-90°x).[5] During the experiments, vinyl-[1-13C]-acetate-d6 (VA) and vinyl-[1-13C]-pyruvate-d6 [6] were hydrogenated to ethyl-[1-13C]-acetate-d6 (EA) and (VP) formed ethyl-[1-13C]-pyruvate-d6 (EP) correspondingly in

acetone-d6 in the presence of a rhodium-based catalyst and 80% enriched pH2 within 8s.

13C RARE MRI was acquired right after SOT.

Results: 13C-HP of 28% and 19% were obtained for EA (80mM, 5mM catalyst) and EP (20mM, 5mM catalyst), respectively, at 90°C and 30bar pH2 pressure after 7s total hydrogenation time. These results were preceded by extensive optimization and analysis using VA.

Discussion and Conclusion: 13C-polarizations of pyruvate and acetate precursors observed in situ here are very promising. If 100% enriched pH2 were used, the HP would increase by a factor of  $\approx$ 1.4. We expect that the yield can be improved by more efficient pH2 dissolution using an H2 sparger or pH2-presaturated method.[7] For biomedical applications, fast side-arm cleavage, and solution purification need to be achieved. SAMBADENA of PHIP-SAH precursors of acetate and pyruvate was demonstrated and may likely be improved further along with improved pH2 dissolution and enrichment. Considering the low (additional) cost, small footprint,[8] high sample throughput,[3] and fast in vivo administration, SAMBADENA holds great promise.

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#### SOLID STATE PHOTO-CIDNP NMR APPLYING BIOMIMETIC DYADS

**RT 47** 

CIDNP and ONP (incl NV centers)

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Photochemically induced dynamic nuclear polarization (photo-CIDNP) enhances NMR intensities by perturbing the nuclear spin system. Time-resolved photo-CIDNP spectra provide insights into radical pair reactions and transient radicals. In solid-state systems, photo-CIDNP was observed in photosynthetic reaction centers using solid-state NMR. The effect in solids is attributed to three-spin mixing, differential relaxation, and decay mechanisms. However, a comprehensive understanding is still a subject of ongoing research.

Our study aims to explore photo-CIDNP in a molecular system using synthetic dyads with a polyproline type II (PPII) helical structure. PPII helices are common in nature and are found in collagen and globular proteins. We postulate that these dyads, incorporating a flavin group, may exhibit the photo-CIDNP effect. The dyads have varying donor-acceptor distances and different spatial orientations, and the initial series is currently under scrutiny.

To conduct time-resolved experiments, we plan to employ field-dependent photo-CIDNP investigations with magic angle spinning NMR techniques. We will use a third harmonic Nd:YAG pulse laser (355 nm) and an opto-parametrical oscillator capable of generating wavelengths from 405 to 2750 nm. The OPO's wavelength will match the absorption maximum of the relevant flavin compound in the blue-light region.

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### DIRECT DETECTION OF THE HYPERPOLARIZATION OF [1-13C]-PYRUVATE VIA PARAHYDROGEN INDUCED POLARIZATION BY SIGNAL AMPLIFICATION BY REVERSIBLE EXCHANGE AT ULTRA-LOW FIELD

**RT 48** 

PHIP

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One of the greatest challenges of NMR to overcome is its low sensitivity, which is directly proportional to nuclear spin polarization. Hyperpolarization techniques address this by being able to increase the nuclear polarization of a molecule of interest from the range of ppm or lower to the percentage regime. One such technique of interest is signal amplification by reversible exchange in shield enables alignment transfer to heteronuclei (SABRE-SHEATH). A key feature of this technique is that the hyperpolarization develops spontaneously in a Bo holding field that is only on the order of 100s nT, in contrast to the mT fields necessary for other SABRE techniques, and the T fields, common to other hyperpolarization techniques. Typically, in order to perform detection in NMR, the nuclear magnetisation of the sample is rotated perpendicular to the Bo field, either via an rf pulse, or by non-adiabatic field switching. This is usually necessary, due to the orders of magnitude smaller magnetic flux density attributable to the sample vs. that of the Bo holding field. This, combined with the lack of detector sensitivity to such small variations in flux density and drifts in B<sub>0</sub>, due to vibrational noise, which are often larger than the magnetic flux density from the sample, makes direct detection of sample magnetisation usually infeasible.

Here, we operate a highly sensitive, single order, SQUID-based gradiometer in the ultra-low, low-noise SHEATH field. Through this setup, we are able to directly detect the pT DC changes in samples hyperpolarized with SABRE-SHEATH, without any field switching or rf pulses. We applied this methodology to a sample of [1-13C]pyruvate, Ir-IMes catalyst and DMSO in methanol. The sample was hyperpolarized, using SABRE-SHEATH by bubbling 99% parahydrogen gas through the sample at a rate of 2 sL/h in a Bo field on the order of 100s nT. Direct detection was performed by measuring the DC magnetic flux density of the sample, while parahydrogen was periodically supplied into the sample. An increase in longitudinal, magnetic flux density on the order of pT was observed, as a result of SABRE-SHEATH, and the corresponding decrease was detected, during the signal decay. Additionally, using the averaged data, it was possible to fit a first order exponential function to determine the buildup and decay time constants that were on the order of 10s of seconds for SABRE-SHEATH. This demonstrates how this direct detection technique can be used to make measurements of these time constants faster and more simply than with traditional methods in the future.

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#### ALTERED METABOLISM IN ANTIBIOTIC-TOLERANT BACTERIA

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As consumption of antibiotics grows and the discovery of effective antibiotic compounds declines, new strategies for impeding resistance are greatly needed. By temporarily changing their metabolic state, bacteria can become tolerant to antibiotics for the duration of treatment and reemerge once the antibiotic pressure is removed [1]. Undetected tolerance in bacteria causes the relapse of diseases and facilitates the development of resistance [2]. Recent studies show that the metabolism of tolerant bacteria reactivates when presented with nutritional supplements, such as amino acids, TCA-related metabolites, and nucleotides. Upon boosting the metabolism, the susceptibility of the bacteria to antibiotics is restored, making the metabolism an attractive target for novel antibiotic therapies [3].

Mass spectrometry methods are known to be sensitive for profiling of bacterial metabolism, but require the extraction of metabolites prior to measurement thus killing the bacteria in the process [4]. Hyperpolarization with the dissolution dynamic nuclear polarization (dDNP) technique yields >10,000-fold signal increases for NMR-active nuclei (e.g., 13C) which allows direct real-time observations of biochemical pathways in living cellular systems [5]. Using non-invasive real-time dDNP-NMR as a method to screen for metabolic changes in commensal and pathogenic gut bacteria, we aim to understand the effect of antibiotic treatment on bacterial metabolism and the impact of mimicking in vivo conditions.

We investigated the impact of antibiotic treatment on the bacterial metabolism by growing E. coli MG1655 in gutmimicking media under ampicillin- or gentamicin-treatment followed by dDNP-NMR-analysis. We also developed ampicillin-tolerant E. coli and Salmonella strains through laboratory evolution experiments to compare them with the susceptible wild type strains. Real-time kinetics showed that treatment with either type of antibiotic impacts the glucose consumption rate and causes metabolic shift of E. coli MG1655.

Bacterial metabolism is tightly linked to antibiotic efficacy. Our results show that dDNP-NMR can provide information on changes in metabolism that occur upon antibiotic interaction and differences between tolerant and susceptible bacterial strains, which can potentially lead to new targets for antibiotic intervention.

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#### EFFICIENT DYNAMIC NUCLEAR POLARIZATION AT HIGH FIELD AND FAST MAGIC ANGLE SPINNING FROM TAILOR-DESIGNED BINITROXIDES

**RT 50** 

#### MAS-DNP

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#### TinyPol radicals optimized from key molecular design principles yield high DNP enhancements at 18.8 T and 65 kHz MAS.

Dynamic Nuclear Polarization (DNP) has proved to be a valuable technique to drastically enhance the sensitivity of Magic Angle Spinning (MAS) solid-state NMR experiments. At the heart of the technique are the Polarization Agents (PAs), whose structure determines the polarization transfer mechanism and the overall efficiency of the DNP process. At 9.4 T, PAs such as the binitroxides AMUPol [1] and TEKPol [2] lead to enhancement factors of up to about 250 at 100 K. Recently, the introduction of PAs with stereo-controlled conformation around the nitroxide, like HydrOPol [3], have shown enhancements as high as 330. Transposing these tremendous sensitivity boosts to the highest fields and fastest MAS frequencies available today is one of the key challenges of modern solid-state DNP.

While hybrid biradicals such as HyTEKs [4], SNAPols [5] or PyrroTriPols [6], recently appeared as promising PAs for DNP at high magnetic fields, parallel efforts have been recently devoted refining the structure of binitroxides in order to make them suitable for high-fields and fast MAS, which resulted in the introduction of the TinyPols [7] and AsymPolPOK families [8].

Here, by using key design principles established for binitroxides at intermediate magnetic fields, we fine-tuned the molecular structure of TinyPol radicals to further improve their efficiency. Notably, by introducing geometries that promote 1H-1H spin-diffusion in the vicinity of the electrons and incorporating recent concepts such as the stereo-controlled conformations, new structures are presented that yield enhancements >200 at 65 kHz MAS and 18.8 T with the best radical of this new series, M-TinyPol(OH)4. Molecular dynamic simulations are applied to refine our understanding of the relation between structure and activity of these radicals. Applications on challenging materials will also be presented.

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#### INVESTIGATION OF 13C STATIC DNP OF P1 CENTERS IN DIAMOND AT 13.8 T AND 6.9 T USING ELDOR AND PULSED EPR EXPERIMENTS

**RT 51** 

General theory, General Instrumentation, MAS-DNP, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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#### <sup>13</sup>C-DNP sweep and pulsed-EPR spectrum of P1 centers in diamond at 13.8 T.

Dynamic Nuclear Polarization (DNP) was shown to enhance Nuclear Magnetic Resonance (NMR) signals by orders of magnitude, vastly expanding the range of NMR applications. For the largest benefits, DNP must be performed at high magnetic fields where the resolution and information content of NMR are maximal.

Understanding DNP quantum mechanics requires knowledge about electron spin dynamics, available only through Electron Paramagnetic Resonance (EPR) experiments, such as electron-electron double resonance (ELDOR).[1-3] Since electron spin properties are field-dependent they must be performed at high fields characteristic of DNP. However, the required high-field EPR instrumentation is commercially unavailable, making the relevant data unobtainable.

Over the past four years, our group constructed a dual DNP/EPR spectrometer, operating at 13.8 and 6.9 T, capable of multinuclear static DNP, continuous wave EPR, pulsed EPR, and ELDOR. Using these new capabilities we investigate the 13.8 T DNP mechanisms in substitutional nitrogen centers in diamond (P1 centers). P1 centers were recently shown to provide efficient hyperpolarization at room temperature and 3.3 T. Their DNP lineshape analysis by Shimon et al. suggests the presence of multiple DNP mechanisms.[4] We present the first hyperpolarization results using P1-DNP at 13.8 T and show that in this field too, P1-DNP is very efficient, and is mediated by multiple mechanisms in a complex interplay.

The 13.8 T P1-EPR spectra reveal an unexpected broad signal with fast relaxation between the sharp P1 peaks, centered around the same g-factor. We assign it to exchange-coupled P1 centers, and using ELDOR experiments, show they provide an efficient mechanism for electron-electron spectral diffusion (eSD) by connecting populations

of different crystallographic sites and <sup>14</sup>N states. At 13.8 T a strong state mixing occurs between the <sup>14</sup>N hyperfine levels resulting in even stronger eSD due to the presence of the forbidden transitions.

This work shows the importance of the previously unnoticed P1 population for DNP due to strong eSD which allows for cross-effect (CE) and truncated CE DNP mechanisms. Thus we show that EPR results acquired under DNP conditions are indispensable for the identification of the active DNP mechanisms.

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#### DESIGN AND APPLICATION OF PHOTO-CIDNP MOLECULAR PROBES

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#### Molecular design of CIDNP probes for monitoring enzymatic hydrolysis reactions

Photochemically induced dynamic nuclear polarization (Photo-CIDNP) is one of the non-invasive hyperpolarization techniques that enhance nuclear spin polarization by light irradiation alone. The mechanism of photo-CIDNP is based on spin sorting during photoreactions, including radical pair formation. Fortunately, some biologically important molecules can serve as suitable electron donors. Thus, photo-CIDNP is a new analytical tool for biomolecules.[1]

On the other hand, the application of photo-CIDNP to MRI is still under development. In-situ photo-CIDNP has been demonstrated in MRI systems and has successfully visualized hyperpolarized molecules [2], but its targets were limited to simple solution systems. The next step is how to obtain valuable information from photo-CIDNP enhanced MRI, such as the presence of specific molecules and reactions.

Here we propose the molecular design of the "CIDNP probe" as a new generation of molecular sensors. Porphyrin derivatives were chosen as chromophores because of their excellent photostability. Next, phenol derivatives, which are known to exhibit high CIDNP performance in combination with porphyrin derivatives, were selected as electron donors. In these pairs, the electron donor units are expected to be strongly enhanced. Then fluorine was added to the electron donor units as the probing units. Finally, the electron donor unit was protected with an acetyl group. In this case, the photo-CIDNP is inactivated because radical formation at the electron donor unit is inhibited, but can be activated by enzyme-catalyzed deprotection. Thus, the newly designed CIDNP probe is an effective sensor for detecting enzymatic reactions. In addition, this CIDNP probe can easily switch target reactions by changing the structure of the protecting group.

CIDNP probe was synthesized, and enzymatic reaction monitoring was demonstrated. CIDNP experiments were performed with benchtop NMR. When the CIDNP probe was not deprotected, no signal enhancement was observed upon light irradiation. When lipase, which catalyzes the hydrolysis reaction, is added, deprotection proceeds and a signal enhancement by CIDNP is observed. This signal intensity enhancement allows for successful monitoring of the reaction. This is an important first step toward new applications of photo-CIDNP for medical diagnosis using

MRI.

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#### RELAXATION MECHANISMS FOR EFFICIENT DNP IN THE LIQUID STATE AT HIGH MAGNETIC FIELDS

General theory, General Instrumentation, Liquid DNP, Loss of hyperpolarization & relaxation

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Dynamic nuclear polarization (DNP) in liquid state holds the potential to greatly increase the sensitivity of NMR and, in a few cases, it is capable of increasing 13C-NMR signals more than 100-fold at high magnetic fields ( $\geq$  3.4 T) [1]. In contrast to solid-state NMR where DNP is a well-established tool, DNP in the liquid state is still in a phase of mechanistic exploration. The polarization transfer in liquids is driven by electron-nuclear cross-relaxation, a mechanism known as Overhauser effect (OE-DNP). The efficiency of OE-DNP strongly depends on the molecular dynamics of the chosen target molecule/polarizing agent (PA) system as well as on the external magnetic field. When the polarization transfer is driven solely by dipolar relaxation, like in the case of 1H nuclei, the efficiency of the process drops significantly at magnetic fields > 1 T [2]. This makes 1H-DNP unattractive at magnetic fields that are interesting for high-resolution NMR spectroscopy.

This limitation does not hold if other target nuclei, such as 13C, 15N, 19F, 31P, are chosen. In those cases, the enhancements in liquids at ambient temperature and pressure are still sizable at magnetic fields >3 T [3,4]. Here we present an overview of our recent understanding of the polarization transfer mechanisms via scalar relaxation between the unpaired electron and the target nuclei. Collisional dynamics mediated by either hydrogen bonds, halogen bonds, or other non-covalent interactions lead to a modulation of the hyperfine coupling on the timescale of a few picoseconds and lower [1]. We examined the case of two model systems, i.e. CHCl3 [6] and triphenylphosphine [5], which give exceptionally high enhancements at high fields (up to 14.1 T) on 13C and 31P, respectively. Finally, we present some preliminary results on hyperpolarization of 15N at room temperature and ambient pressure at 14.1 T. Our results support the hypothesis that non-covalent interactions between target molecules and polarising agents are effective in boosting the NMR enhancements.

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#### PRELIMINARY 19F RESULTS OF THE WORLD'S FIRST HFX SOLID-STATE MAS DNP PROBE

RT 54

MAS-DNP

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Solid-state nuclear magnetic resonance (NMR) spectroscopy is a powerful tool for investigating the structures and dynamics of pharmaceutical formulations. In particular, fluorine-19 (19F) NMR is commonly used to study drug molecules, excipients, and polymers due to the abundance of fluorine in these materials. However, the sensitivity of 19F NMR is often limited, which can make it challenging to detect low levels of impurities or study small sample sizes. Dynamic nuclear polarization (DNP) is a technique that can enhance NMR signals by transferring the polarization from electron spins to nuclear spins. In recent years, DNP-enhanced 19F solid-state NMR has emerged as a promising approach for studying pharmaceutical formulations and biological systems. By increasing the sensitivity of 19F NMR, DNP allows researchers to detect smaller quantities of drugs and excipients, and to study the dynamics of these materials at a molecular level. One of the advantages of 19F NMR spectroscopy is that it is often background-free. Unlike other nuclei, such as 1H or 13C, which can give rise to broad overlapping signals from excipients or other cellular components, the 19F signal is typically only observed from the molecule of interest. This makes 19F NMR particularly useful for studying pharmaceutical formulations, where it allows researchers to focus on the behavior of the drug molecule itself, without interference from excipients or other components of the formulation. Similarly, in-cell 19F NMR can be used to study the behavior of specific biomolecules within cells, without interference from other cellular components. In this presentation, I will share the preliminary results from 19F DNP NMR experiments obtained using the world's first HFX probe designed by Bruker within the PANACEA consortium. This is an exciting development in the field of NMR spectroscopy. By combining DNP with 19F NMR, we can obtain detailed information about the structure and dynamics of molecules in pharmaceutical formulations and biological systems.

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# TWO-PHASE TRANSFER CATALYSIS FOR SABRE-BASED NUCLEAR SPIN HYPERPOLARIZATION

RT 55

Applications, PHIP

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# 19F NMR spectroscopy allows unambiguous assignment of fluorinated signals to the corresponding solvent phase.

Parahydrogen-based nuclear spin hyperpolarization is currently one of the most promising signal enhancement methods with respect to future biomedical applications. While Signal Amplification by Reversible Exchange (SABRE) is a reproducible method, the transfer of the hyperpolarized molecules into biocompatible solvents remains a problem. Regarding this, two-phase transfer catalysis could be an important approach. In such a setup, hyperpolarization would occur only in an organic solvent in which the catalyst would be selectively dissolved. However, the hyperpolarized molecules would also be able to diffuse into an adjoining aqueous phase, due to their miscibility in both organic and protic solvents, where they could then be removed in the aqueous phase without contamination.

We demonstrate these by having performed 1H and 19F nuclear spin hyperpolarization experiments on fluorinated molecules, which are excellent for rapid concentration detection via 19F NMR spectroscopy. Measurements on a Bruker wide bore 7T NMR spectrometer show on the example of 6-fluoro-3-hydroxy-2-pyrazinecarboxamide (= anti viral drug favipiravir[1-2]), which is both soluble in CDCl3 and D2O, the significant effects of its conformational changes and its distribution in the two solvents These were detected from changes in chemical shift and/or phase changes in 19F NMR signals. For the two-phase transfer measurements, 1mL of organic solvent, containing Ir-catalyst and 1mL of aqueous solution were used (10mm NMR tube). The organic phase was initially colored yellow from the catalyst, which then turned reddish after activation with hydrogen (50% enrichment). Depending on the catalyst used, this led to changes in the phases of the hyperpolarized signals. Positive signal enhancements in the 1H

NMR spectrum were observed with Crabtree catalyst, whereas negative signal enhancements in the 1H NMR spectrum were observed with the IrIMes catalyst with an otherwise identical sample composition. The exact opposite observations were detected in the 19F NMR spectra. Interestingly, observations, such as this phase inversion, can be used for determining the phase boundary (CDCl3/D2O) of the two-phase system. Furthermore, in the case of favipiravir, conformational changes were detected in the aqueous phase, while in methanol and chloroform only one form is present, indicating Not every conformer of molecules are hyperpolarizable.

These results indicate that two-phase transfer catalysis is a promising approach for parahydrogen-based hyperpolarization techniques.

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#### USING MEOP HYPERPOLARIZED 3HE FOR IMPROVING PRECISION IN MAGNETIC FLUX DENSITY MEASUREMENT

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Currently the methods to disseminate the unit Tesla, the standardized physical quantity of magnetic flux density, are based on NMR measurements on thermally polarized proton nuclear spins in water samples [1]. Due to the low SNR of the water sample at low fields (<2mT) and an absorption technique used at fields above, the relative measurement uncertainty is limited to a range of  $10^{-4}$  to  $10^{-6}$ . Since hyperpolarized 3He gas offers increased SNR and long precession times (T2\*) [2], it has the potential to reach a higher precision in magnetic field metrology, over a broader field range, as was shown in high field measurements [3]. Using metastability exchange optical pumping (MEOP) to create the hyperpolarization [4] promises fast buildup times and avoids the back-action of other polarized atoms on the 3He precession [5].

We will present the MEOP setup and first measurements, which were performed inside a table-top four-layer magnetic shield with integrated coils to generate a constant B0 in the order of  $\mu$ T, as well as a perpendicular and resonant B1 field to flip the magnetization initiating 3He spin precession. Our 3He MEOP system includes an HF resonator driving the plasma in a spherical 3He filled cell (~ 2 cm diam.) to create metastable 23S1 states. A circular polarized laser beam is used to polarize the electron spins and then transfer to nuclear spins of 3He. By using a commercial Rb optical magnetic gradiometer (2.3 cm baseline), we were able to measure the precession of the 3He magnetization and deduce the Larmor frequency at different B0 magnetic field strengths and for varying flip angles. This allowed measurements of polarization, buildup times as well as T1 and T2 relaxation times and to study the systematic effect of 3He polarization on the detected Larmor frequency. These first results give rise to future setup improvements aiming to fully characterize and thus minimize frequency measurement uncertainties. To validate the precision of our setup, we plan to further do measurements in a large magnetically shielded room in combinations with SQUID detection, which provides a more stable field environment and allows 50 times higher SNR [2]. This would also allow the comparison of different sensors.

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### PHIP OVER HETEROGENEOUS CATALYSTS – THE ROLE OF CARBIDE PHASES AND ORTHO-PARA CONVERSION

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Parahydrogen-induced polarization (PHIP) is based on the conversion of correlated spin order of parahydrogen (p-H2) into polarization of a target molecule via catalytic hydrogenation. However, for a successful observation of PHIP effects in the NMR spectra of hydrogenation products, hydrogenation with p-H2 must occur via pairwise addition route – i.e., two H atoms from the same p-H2 molecule should end up in the same product molecule. The observation of PHIP with the use of heterogeneous catalysts in 2008 indicated the existence of hydrogenation mechanisms in which the correlation of hydrogen atoms on the surface of the catalyst is preserved, even though this is in disagreement with the well-accepted mechanisms. However, despite extensive research, there is still no definite understanding of the nature of the HET-PHIP phenomenon.

Nowadays, special attention is paid in the field of heterogeneous catalysis to various metal carbides. It was also speculated that different carbonaceous deposits, formed during the reaction on the catalytical surface, can alter the hydrogenation mechanism itself. In this work, we have studied two carbides – Rh2C and two-dimensional Mo2C – in hydrogenation of propyne and propene with p-H2. A direct comparison between carbide and metallic phases of rhodium was performed, while Mo2C was compared to Rh/TiO2 (one of the best catalysts for HET-PHIP) under the conditions of similar catalytic activity. The results indicate that, while carbides do provide some selectivity to the pairwise addition route, the carbide phase apparently isn't the key to the HET-PHIP.

In addition, we have also taken a look at the conversion of parahydrogen to normal hydrogen on the surface of the Rh/TiO2 catalyst in the reaction by NMR. It was found that the presence of molecules of hydrocarbon, the hydrogenation substrate itself that is present on the catalytical surface regardless of the type of the catalyst, can significantly affect ortho-para conversion of H2. Without the substrate, the ortho-para conversion is higher than in the presence of a substrate during the reaction, and this effect is more pronounced for propyne hydrogenation – hinting to the conclusion that even in the excess of hydrogen in the hydrogenation mixture the catalyst surface isn't covered by it.

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### BULLET-DISSOLUTION DYNAMIC NUCLEAR POLARIZATION AND LIGAND BINDING

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Dissolution/Melt DNP

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This figure demonstrate the enhancement factor in proton signal as a result of Hyperpolarization.

In bullet DNP, a sample is hyperpolarized at cryogenic temperatures and rapidly transferred to a second magnet where it is dissolved and liquid-state nuclear magnetic resonance (NMR) spectra are recorded [1,2]. Bullet-DNP has advantages for observing ligand-binding since it is scalable to small solvent volumes and thus reduces the required amount of protein. Here we present ligand-binding experiments, in which the sensitivity of the hyperpolarized signal detection is improved further via a 13C-1H reverse INEPT polarization transfer from carbon to methyl protons.

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### **Christopher Pötzl**



# RT 59

### COMBINING DDNP WITH GIPAW CALCULATION TO DETERMINE THE STRUCTURE OF SHORT-LIVED INTERMEDIATES.

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Hyperpolarized/TE 1 0.9 0.8 0.5 0.7 0 171 0.6 5 170 10 15 20 25 168 169 v 0.5 **Evolution of AUC** 0.4 0. 0.3 0.2 0 4 0.1 0.2 0 165 170 20 15  $\delta(^{13}C)$  / ppm

dDNP experiment with a final concentration of 37.5 mM pyruvate and 93.75 mM  $\rm Ca^{2+}$ 

Calcium pyruvate clusters used for chemical shielding calculations



#### dDNP spectrum and pyruvate clusters

Dissolution dynamic nuclear polarization experiments are typically recorded as a series of one-dimensional spectra using small flip-angle detection pulses. While excellent signal intensities and time resolution, the structural information provided by these detection schemes is limited. This is particularly challenging, when the structure of the detected compound, e.g., transiently formed intermediates with short lifetimes, is not known.

Here we suggest a possible route to overcome this limitation by computing chemical shifts of hyperpolarized intermediates by means of ab-initio molecular dynamics simulations coupled to GIPAW chemical shielding calculations. Such the NMR signatures of a detected compound can be computed based in a structural model and

matched against the experimentally observed chemical shifts.

We demonstrate the suggested approach using calcium pyruvate (CaPy) as a model system. CaPy readily forms in solution, and it is currently hypothesized that is the active form of pyruvate in mitochondrial environments. To obtain chemical shifts of transiently formed CanPym clusters, we hyperpolarized pyruvate and mixed it upon arrival at the NMR spectrometer with Ca2+ solutions. Within a minute the cluster formation could be observed via the appearance of a second signal next to that of free pyruvate.

To determine the structure of the clusters, several MD simulations were performed with different concentrations of Ca2+ and pyruvate ions. Interestingly, in all calcium pyruvate simulations, regardless of the conditions, the simulations contained calcium pyruvate clusters with stoichiometries of 1:2 and 2:4. Computing chemical shifts by GIPAW for a representative set of structures and averaging the results, we could qualitatively reproduce the experimentally observed chemical shift of the CanPym clusters, and thus determine the structure of the observed intermediates before calcium pyruvate precipitation led to a stable sample.





### SPYING ON PARAHYDROGEN-INDUCED POLARIZATION TRANSFER USING A HALF-TESLA BENCHTOP MRI AND HYPERPOLARIZED IMAGING ENABLED BY AUTOMATION

**RT 60** 

Dissolution/Melt DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation

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### 13C FLASH MRI acquired in situ right after the polarization showing the reaction chamber (left) or after shuttling to the second tube with a a phantom (right, "rotes Ampelmännchen").

Portable, cost-efficient devices for the hyperpolarization of nuclear spins are not available, hindering the transfer of hyperpolarization to routine use in laboratories and medical centers. Here, we developed a portable, automated polarizer based on parahydrogen-induced hyperpolarization (PHIP) at an intermediate magnetic field of 0.55 T.

The core of the system is a "teaching MRI" with a half-Tesla permanent magnet with 50-100 Hz homogeneity and non-negligible drift (PureDevcies, Würzburg). Still, we were able to demonstrate semi-continuous, fully-automated hyperpolarization of 1H in ethyl acetate-d6 and ethyl pyruvate-d6 of 14.4% and 16.2%, respectively, and a 13C polarization of 1-13C-ethyl pyruvate-d6 of 7%. The duty cycle for the preparation of hyperpolarization was as short as 1 min, and the footprint of the system was about 1 m2.

To reveal the full potential of 1H hyperpolarization in such an inhomogeneous and unstable magnetic field, we converted the anti-phase PHIP spectrum into an in-phase spectrum with out-of-phase echo, thereby increasing the SNR by 5. Interestingly, at half a Tesla magnetic field, essentially all vicinal protons are approaching the strong coupling regime. This effect causes a spin evolution that is more complex compared to high magnetic fields, where

the coupling is weak.

To optimize the polarization under these challenging conditions, we monitored the spin order evolution in real time by conducting the hydrogenation and spin order transfer within the MR system and monitoring the evolution using spin-echos. This approach allowed us to save expensive, custom-made reagents and drastically accelerate optimization.

After the hydrogenation, the hyperpolarization was transferred from 1H to 13C using the ESOTHERIC sequence. The intense 13C polarization of 1-13C-ethyl pyruvate-d6 allowed us to acquire images of the reaction chamber and a phantom in situ ( "rotes Ampelmännchen", 0.3125 mm x 0.3125 mm spatial resolution). We will use this approach to pursue further the translation of hyperpolarized MRI for in vivo applications.





THE STUDY OF 13C SOLID-STATE PHOTO-CIDNP EFFECT ON SITE-DIRECTED MUTATED FLAVOPROTEIN MR4511-C71S

**RT 61** 

CIDNP and ONP (incl NV centers)

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Structural model of the LOV domain Mr4511-C71S highlighting the position of near-by tyrosine.

Low sensitivity remains a major limiting factor for the wide applications of nuclear magnetic resonance (NMR) spectroscopy in different areas. The chemically induced dynamic nuclei polarization (CIDNP) is one of the hyperpolarization methods which generates non-Boltzmann nuclear spin magnetization upon illumination, allowing for sensitivity enhancement in NMR [1]. Several studies have investigated the solid-state photo-chemically induced dynamic nuclear polarization (photo-CIDNP) effect in the flavoprotein system, however the studies were restricted in tryptophan-FMN radical pair system and the mechanisms underlying this effect have yet to be fully understood [2][3][4]]5]. Previous studies on tryptophan-lacking light-oxygen-voltage (LOV) domain 4511 from Methylobacterium radiotolerans (Mr4511) shows that besides tryptophan, tyrosine can also act as electron donor and forms a radical pair with the FMN leading to the solid-state photo-CIDNP effect. This study involving site-directed mutants of the flavoprotein Mr4511-C71S by comparing the photo-CIDNP effects observed in the mutated protein with those of the wild-type protein. The characterization reveals that the distance between tyrosine and FMN, as well as the orientation of tyrosine, exert a significant influence on the generated photo-CIDNP effect, it suggests that the four tyrosine residues in close proximity to FMN within the flavoprotein system may play a collective role in the photo-CIDNP generating process. The investigation indicates that the tyrosine residue at position 104 in the flavoprotein system plays a crucial role in the binding with FMN, since a sharp FMN occupancy decreasing was observed in the Y104 lacking mutant. Additionally, the investigation also allows for the estimation of the shielding effect that occurs between the four tyrosine residues themselves.

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### PARTIALLY NEGATIVE LINE OF ORTHOHYDROGEN RESONANCE IN SIGNAL AMPLIFICATION BY REVERSIBLE EXCHANGE

**RT 62** 

PHIP

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Singla Amplification by Reversible Exchange (SABRE) is an important hyperpolarization method utilizing the unique properties of parahydrogen (p-H2) molecules, which can induce hyperpolarization in other molecules.[1] In the SABRE protocol, activation processes occur where the precatalyst, p-H2, and a ligand react together, resulting in the rearrangement of the precatalyst structure into its final form - the catalyst. The catalyst, molecule, and p-H2 form a labile complex in which hyperpolarization is induced in the molecule. The complex is labile, and upon release, the molecule retains hyperpolarization. The catalyst can next involve the next molecule and p-H2, and the hyperpolarization cycle can be repeated. Extensive studies concerned with SABRE have focused on issues concerned with the efficient hyperpolarization of molecules. As for the fate of the released p-H2, it is converted into orthohydrogen (o-H2), exhibiting a typical single Lorentz resonance. However, in some cases, the resonance of the released o-H2 shows a Partially Negative Line (PNL)[2] pattern.[3] We have identified the conditions under which SABRE can yield PNL. We have also investigated the occurrence of PNL in SABRE using various combinations, ligands, and solvents. For the investigated systems, we found that PNL could only be observed during the activation processes, and not thereafter. We hypothesized that a specific temporary hydride species created during the activation process is directly associated with the occurrence of the PNL effect.

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### EXPLORING THE SCOPE OF NHPHIP HYPERPOLARIZATION IN METABOLITE ANALYSIS IN HUMAN BIOFLUIDS

RT 63

Applications

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Parahydrogen hyperpolarization offers a relatively accessible way of increasing NMR signals by approximately three orders of magnitude over what is offered by the regular means of NMR sensitivity. This potentially opens new application avenues in biofluids analysis, giving access to metabolites and metabolic information below the Limit of Detection (LoD) of contemporary NMR. However, combining nhPHIP, a parahydrogen hyperpolarization technique that is based on reversible chemical interactions between an organometallic catalyst and analytes, with the complexity of biological mixtures is challenging.

The basic approach for nhPHIP of urine samples was established 7 years ago [1] and we have worked towards developing proof-of-concept applications. E.g., nhPHIP was applied in a pharmacokinetics study [2], where mid-nanomolar concentrations of a drug and its metabolites were detected and quantified in urine samples. Further, it was shown that parahydrogen hyperpolarization is robust enough for compiling spectral libraries for assignment of hyperpolarized signals [3] and that it can be applied to minimally treated urine, producing highly information rich hyperpolarized NMR spectra [4].

In terms of prospective applications in the clinical or diagnostic domains, however, blood is often a more relevant

biofluid. Therefore, we have been working towards adapting nhPHIP to blood samples, which is a very different sample matrix. It mandates new approaches for sample preparation and poses chemical challenges that were not observed for urine samples. Herein, we present the current status of our work towards applying nhPHIP to blood, to expand the scope of biological matrices that can be analyzed by parahydrogen hyperpolarization.

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### HIGH-FIELD NON-HYDROGENATIVE PHIP (HF-NHPHIP) FOR THE ANALYSIS OF HUMAN AND VETERINARY URINE SAMPLES

**RT 64** 

General theory, Applications, PHIP, Dissolution/Melt DNP, Liquid DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation

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### pH2 derived hyperpolarized hydrides HA and HX are detected, while pH2 and substrates (an analyte or a cosubstrate) reversibly associate with the catalyst.

High-field non-hydrogenative PHIP (HF-nhPHIP) [1] is a chemoselective method that can detect more analyte classes than previously expected. By finetuning the system and/or choosing an appropriate sample preparation technique it is possible to force specific analytes into binding the Ir-IMes catalyst. This enables to move from detection of pyridines and pyrazines among others to amino acids and oligopeptides. HF-nhPHIP can guide complex mixture analysis [2-4] by giving an estimation of presence and concentration of different molecules in the sample.

In my talk I will compare human and veterinary urine samples measured with HF-nhPHIP technique. Previously, we have shown the richness of analytes in human urine analyzed by HF-nhPHIP, when specific sample preparation protocols are applied [2, 3]. Now we combine this knowledge with finetuned HF-nhPHIP chemosensor to analyze and compare human and canine urine. Although thermally polarized NMR has been used to classify urine samples based on species, our work aims to provide applications for pH2 hyperpolarization. We believe that with further research and development, HF-nhPHIP could be used to map metabolites and metabolomic pathways that fail to be detected with common analytical tools.

I will show that the chemical shifts of complex biological molecules with multiple ligation sites like amino acids and oligopeptides [5] are clearly distinguishable from monodentate N-heteroaromatics in HF-nhPHIP measurements. I will demonstrate how HF-nhPHIP catalyst cosubstrates 1-methyl-1,2,3-triazole (mtz), pyridine and 3-fluoro-4methylpyridine can be used for detecting specific analyte classes in human and canine urine samples.

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## INCREASING THE HYPERPOLARIZATION LEVEL ON FULLY BIOCOMPATIBLE PARAHYDROGEN POLARIZED PYRUVATE

**RT 65** 

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13C polarization on pyruvate ester (AllyI-Pyr) and sodium Pyruvate, using different conditions: A) high catalyst concentration, linear MFC profile; B) low catalyst concentration, linear MFC; C) low catalyst concentration, tailored MFC.

Hyperpolarized [1-13C]pyruvate obtained by means of the PHIP-SAH (Side Arm Hydrogenation) method has already been used to carry out metabolic studies in cells and in-vivo, although the aqueous solution of the HP metabolite still contained a non-neglectable concentration of organic solvents (ethanol and CDCl3) and metal catalyst. When the hydrogenation reaction has been carried out in pure chloroform (CDCl3) and the water solution, obtained after the hydrolysis of the ester, was filtered on a lypophilic resin, the toxic contaminants were removed. Nevertheless, being the efficiency of parahydrogen spin order transfer to the hydrogenation product dependent on the hydrogenation solvent, the 13C polarization level on the ester was  $5.5 \pm 0.4\%$  and, after hydrolysis and filtration of the water phase, was  $2.3 \pm 0.3\%$  on sodium [1-13C]pyruvate [O.Bondar et al. Catalysis Today 2022].

The herein reported work has been focused on increasing the 13C polarization level of pyruvate, while keeping a

fully biocompatible aqueous solution of this metabolite. This task has been accomplished by means of an improved hydrogenation catalysis and a tailored Spin Order Transfer (SOT) step.

Concerning the hydrogenation reaction, a lower catalyst concentration leaded to higher polarization on the parahydrogenation product. At the same time, the addition of a phosphine ligand, that acts as an adjuvant of the metal complex, improved the catalyst efficiency and a high concentration of the hydrogenation product was obtained in a few seconds.

The use of a lower catalyst concentration also limited the hyperpolarization loss during hydrolysis. Therefore, using a lower catalyst concentration, the 13C polarization on the ester was 7.2 % and that on sodium pyruvate 4.3 %.

As far as SOT is concerned, the magnetic field cycling procedure has been improved through the application of a remagnetization profile tailored to the J-couplings between the protons and the 13C, instead of a linear profile from 0.05 T to 2 T. This allowed to obtain  $9.5 \pm 0.5$  % polarization on the ester and, in the end the 13C polarization obtained on sodium [1-13C]pyruvate in water was  $5.7 \pm 0.6\%$ .

In conclusion, the significant reduction of the catalyst concentration, together with the application of a tailored MFC procedure, leaded to an increase of the hyperpolarization level on the 13C signal of allyl-[1-13C]pyruvate from the previously reported  $5.2\pm0.6\%$  to  $9.2\pm1.0\%$ . Following to hydrolysis and phase extraction, the hyperpolarization level on the 13C-carboxylate of sodium [1-13C]pyruvate the aqueous solution was  $5.7\pm0.6\%$ , being the previously reported value  $2.7\pm0.6\%$ .



## LARGE 31P-NMR ENHANCEMENTS IN LIQUID STATE DYNAMIC NUCLEAR POLARIZATION

RT 66

Liquid DNP

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### Large 31P-NMR enhancements are observed with DNP in PPh3 doped with BDPA radical, while they are reduced when a nitroxide radical or triphenylphosphine oxide are used instead.

Dynamic nuclear polarization (DNP) can increase the low sensitivity of nuclear magnetic resonance (NMR). Electron spin polarization is transferred from an organic radical to coupled target nuclei under microwave irradiation. In the liquid state, nuclear polarization builds up through a cross-relaxation process called Overhauser effect, which is driven by time modulation of the electron-nuclear hyperfine coupling [1].

Besides 1H and 13C, 31P is also an attractive nucleus in NMR. The molecule triphenylphosphine (PPh3) shows large 31P-NMR signal enhancements ( $\varepsilon > 150$ ) for magnetic fields ranging from 0.3 T to 14 T when doped with BDPA as polarizing agent (PA) [2-4]. To shed light into this unusual field dependence of the enhancement, we compared the 31P-DNP performance of two PAs, BDPA and nitroxide radical TEMPONE (TN), on two target molecules PPh3 and triphenylphosphine oxide (TPPO) in different solvents at 1.2 T. The results show a large 31P-NMR signal enhancement for BDPA/PPh3 in benzene ( $\varepsilon = 360 \pm 36$ ), which decreases upon exchange of the solvent or the PA ( $\varepsilon = 21 \pm 3$  for TN). No enhancement is observed for TPPO as the target molecule.

With the help of DFT calculations, the experimental observations were rationalized as follows: 1) PPh3 tends to form a weak complex through non-covalent interaction, which leads to short distances between 31P and the allyl group of BDPA and therefore a large hyperfine coupling ( $\Delta Aiso > 13$  MHz). 2) The efficiency of TN as PA is hampered by the larger distance to 31P and a reduced hyperfine coupling. 3) In the case of TPPO, the oxygen prevents a close approach of PA and 31P leading to negligible hyperfine couplings [5].

Our study in 31P-DNP showed that a radical and target molecule non-covalent interaction can be effective for large

NMR signal enhancements independent on the magnetic field.

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### Victor RIBAY



### HYPERPOLARIZED 13C NMR SPECTROSCOPY URINE SAMPLES AT NATURAL ABUNDANCE BY QUANTITATIVE DISSOLUTION DYNAMIC NUCLEAR POLARIZATION

**RT 67** 

Dissolution/Melt DNP

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# Hyperpolarized 13C NMR spectroscopy by dissolution dynamic nuclear polarization provides a rich and resolvent 13C metabolic profile on urine samples at natural abundance while retaining precious quantitative information using a standard addition work

NMR-based metabolomics provides important information on complex biological mixtures but mostly relies on 1D 1H experiments for sensitivity reasons. However, strong peak overlap is a limitation for the analysis of inherently complex biological mixtures. To overcome this limitation, 13C NMR benefits from a wider spectral dispersion and narrower signal linewidth but is barely used in metabolomics due to its lower sensitivity. Dissolution Dynamic Nuclear Polarization (d DNP) offers an opportunity to improve significantly the sensitivity of 13C NMR [1]. A preliminary study showed the possibility to detect hyperpolarized 13C signals on plant and cancer cell extracts in a single scan at natural abundance with d-DNP, results that were inaccessible by conventional 13C NMR [2]. Recently, 13C d-DNP has been successfully incorporated into an untargeted metabolomics workflow on plant extracts [3]. However, these studies were limited to relatively concentrated extracts. Here we report, for the first time, the suitability of 1D 13C d-DNP to provide rich information on a biofluid (urine) at natural 13C abundance, and in conditions which are compatible with metabolomics studies [4]. These results were obtained thanks to a multiparametric optimization of the complete d DNP experiment that we recently reported [5]. Furthermore, we show that NMR quantitative capabilities can be maintained with these hyperpolarization experiments, enabling the precise measurement of absolute concentrations of metabolites that are challenging to quantify in 1H NMR due to strong peak overlap. These preliminary results showcase the ability of d-DNP to provide highly resolved and hyperpolarized 13C NMR spectra of biofluids, thus opening promising application perspectives for both untargeted and targeted metabolomics.

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### SETUP OF TIME-RESOLVED PHOTO-CIDNP MAS NMR EXPERIMENTS WITH A PULSED NANOSECOND LASER

**RT 68** 

CIDNP and ONP (incl NV centers)

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In the past, many methods for polarization generation (PG) were developed, improving the sensitivity of NMR by several orders of magnitude by creation of transient highly polarized non-Boltzmann nuclear spin states, also referred to as hyperpolarized states.[1] One of these methods is the exploitation of the solid-state photo-CIDNP (photochemically induced dynamic nuclear polarization) effect, which describes the occurrence of non-Boltzmann nuclear spin polarization in rigid samples upon illumination. The solid-state photo-CIDNP effect leads to strong modifications of signal intensities and, thus, allows for new classes of experiments.[2] In combination with nanosecond laser flash excitation, photo-CIDNP MAS NMR enables time-resolved measurements which give insights into the kinetics of polarization transfer within the observed spin system. Such experiments would allow for detailed studies of the mechanisms that generate the solid-state photo-CIDNP effect.[1]

In order to carry out these time-resolved solid-state NMR measurements, an experimental setup coupling the NMR spectrometer to a nanosecond pulsed laser has to be established. For this setup, synchronization between the NMR pulse sequence and the pulsed laser which operates at a fixed frequency of 10 Hz must be achieved. Synchronization is necessary for the laser flash to be set at a distinct time during the pulse sequence, which allows for polarization build up. This synchronization requires a direct communication between the NMR spectrometer and the laser, which can be realized using TTL connection. The synchronization then can be achieved by exploiting the fact that the Q-Switch of the laser can be triggered externally by the NMR pulse program via TTL.

With this setup, time-resolved photo-CIDNP measurements of e.g. 4-ALA labelled photosynthetic reaction centers from Rhodobacter sphaeroides can be carried out in order to observe polarization build-up and its kinetics.

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## TOWARDS TABLETOP RECYCLABLE HYPERPOLARIZATION WITH A COMPACT FREEZE, MELT, AND FLOW DNP POLARIZER

Dissolution/Melt DNP

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Solidworks modeling of the dual cryostat and heating unit

Hyperpolarization methods provide a way to tackle the inherently low NMR sensitivity and acquire a higher signal intensity in a shorter time. Twenty years ago, dissolution Dynamic Nuclear Polarization (d-DNP) [1] was introduced and is now one of the hyperpolarization methods providing boosts of more than 10'000-fold in sensitivity on a routine basis.

However, this method suffers from two drawbacks narrowing its use. The overall hyperpolarization experiment is i) destructive and ii) single shot. Indeed, the frozen sample, once polarized, is dissolved before being analyzed in liquid state NMR. During this process, it is inevitably diluted, and its signal vanishes within seconds, and it cannot be repolarized due to the dilution. On the other hand, the most valuable NMR experiments rely on repeated acquisition, including incremented time steps for multidimensional acquisition and phase or gradient modulation for coherence selection and error correction. In d-DNP, this is not possible due to the single-shot nature of the experiment.

We are presently working on turning d-DNP into a new version that will be widely compatible with NMR spectroscopy. It consists of replenishing the DNP hyperpolarization of a sample flowing through a closed loop, without dilution nor contamination using hyperpolarizing silica-based material (HYPSO) as polarizing matrices [2,3] in a compact and helium-free DNP polarizer coupled to a benchtop NMR spectrometer for liquid-state detection.

Here, we will present our latest progress on implementing fast freeze and melt of the sample with the design of a dedicated probe composed of a dual cryostat and heating unit and its first performance obtained on a sample of water. This unit will be placed into our DNP polarizer performing at 77K and with a 1T magnetic field on classic samples and porous materials. The current device is for now equipped with a cryostat for static measurements, a double-tuned 1H/13C probe, a 30 GHz and 5W microwave generator, and a nitrogen auto-refill station.



### 200 GHZ SINGLE CHIP DYNAMIC NUCLEAR POLARIZATION MICROSYSTEM

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General Instrumentation

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#### Photo of the single chip DNP microsystem and DNP enhancement curve of 2% BDPA:PS

The single chip integration of the sensitivity relevant part of NMR, ESR, and DNP enhanced NMR detectors is a promising approach to improve the limit of detection, especially for nL and sub-nL samples. During the last two decades, the separate integration on a single chip of the front-end electronics of inductive NMR spectrometers, as well as ESR spectrometers have been demonstrated. Recently, the co-integration on a single silicon chip of the front-end electronics of an NMR and an ESR detector operating at 11 GHz (ESR)/16 MHz (NMR) has been demonstrated [1]. Due to the strong motivations to operate at higher static magnetic fields, in this work we designed and characterized a single chip integrated DNP microsystem operating 200 GHz (ESR) / 300 MHz (NMR). The realized

single chip microsystem generates microwave magnetic fields at 200 GHz, allows to performs continuous wave ESR experiments by field or frequency sweeps, and to perform NMR and DNP enhanced NMR experiments. The maximum microwave magnetic field generated by the ESR oscillator is between 5 to 10 G depending on the biasing condition of the oscillator. DNP enhancements as large as 50 are achieved with 2% BDPA:PS at 15 K. The integration of the microwave source and ESR detector together with the NMR sensor allows to study DNP enhanced NMR without the need of an external microwave source and connections to carry the microwave signals such as waveguides. All the connections to/out of the magnet, where the microwave excitation and ESR detection occurs on chip, are DC. As a result, these single chip integrated ESR, NMR, and DNP-NMR detectors are suitable for the miniaturization of the probe, for the reduction of the losses and complexity of the connections, and for the realization of dense arrays of detectors for parallel (simultaneous) spectroscopy of several samples. Additionally, the single chip approach might allow for a better SNR for volume limited samples in the nL and sub-nL range tightly matched to the sensitive volume of the detector with respect to the conventional bulky inductive probes which are optimized for microliter and larger sample volumes. By suppressing the need for external microwave sources and microwave connections, the single chip approach proposed here reduce drastically the cost and the complexity of the DNP instrumentation and, hence, should allow for a more widespread use and study of DNP methodologies on nL and sub-nL samples.

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### MOLECULAR DESIGN AND THEORETICAL ANALYSIS OF NOVEL POLARIZING AGENT FOR HIGHLY EFFICIENT TRIPLET-DNP IN GLASSY MATRICES

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Triplet DNP

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Dynamic nuclear polarization using photo-exited triplet electron (triplet-DNP) is a technique that can obtain high nuclear polarization under mild condition since high electron spin polarization between triplet sub-levels is achieved regardless of temperature by the spin-selective intersystem crossing [1]. However, due to hyperfine coupling and dipolar interactions between triplet electrons, the electron spin resonance (ESR) linewidth of the triplet is broadened over 100 mT at X-band. By sweeping the magnetic field, spin packets within the sweep range can be utilized for polarization transfer. Nonetheless, the practical limitation for the magnetic field sweep width is approximately 10 mT. As a result, only a limited fraction of spin packets satisfies the Hartmann-Hahn condition.

Previously, triplet-DNP have been focused on controlling the orientation of the polarization agent to suppress ESR broadening caused by dipolar interactions [2]. By utilizing single crystals and precise control of orientation, it has been possible to use almost all spin packets for polarization transfer, leading to the successful achievement of polarization rates of several tens of percent for nuclear spins. However, the implementation of this strategy poses technical challenges, due to the requirement for growing large single crystals on the scale of centimeters and the precise orientation control needed.

In this study, in order to tackle the fundamental challenge of triplet-DNP, we present a chemical approach based on the molecular design of polarizing agents as an alternative to the conventional physical approach of orientation control. The critical parameters of this approach are the zero-field splitting parameters, D and E, which represent the energy gaps between triplet sublevels in the absence of magnetic field and determine the linewidth of the ESR spectrum in the triplet state. The D and E values are related to the average distance between spins and the rhombicity of the zero-field splitting tensor and ESR spectra becomes sharper as D and E become smaller. As a proof of concept, we investigated a series of polarizing agents with the significantly narrow the ESR linewidth through the isotropic delocalization of triplet electrons and successfully exceeds the previous highest 1H polarization of glassy materials with the new polarizing agent. Stare-of-the art quantum calculation reveal the molecular design guideline with the size of D and E values are reduced and the electron spin polarization is increased at the same time.

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PHIP

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Schematics of pairwise addition of parahydrogen to an unsaturated ammonium salt with subsequent polarization transfer from 1H to 14N nuclei

Most of the NMR-sensitive nuclei have nuclear spin  $I > \frac{1}{2}$  and quadrupolar moment inducing rapid relaxation and consequent line broadening in solution-state NMR spectra. Thus, these nuclei are not chosen as hyperpolarization targets, in spite of high natural abundance of many quadrupolar isotopes (e.g., 14N, 35Cl or 11B). Here, we present proof-of-principle demonstration of possibility to hyperpolarize quadrupolar 14N nuclei in solution using parahydrogen-induced polarization (PHIP) technique.

Based on the previously reported relatively long 14N T1 of ca. 2 s for choline [1], we chose unsaturated quaternary ammonium salts as substrates for pairwise parahydrogen addition. Salts with three saturated (methyl, ethyl or propyl) and one unsaturated (vinyl or allyl) moieties were used. Hydrogenation of these compounds was found to be challenging—cationic homogeneous catalyst [Rh(dppb)(NBD)]BF4 showed no activity in the reaction while Wilkinson's catalyst [Rh(PPh3)3Cl] cleaved the salts to form hydrocarbons. Heterogeneous Rh/TiO2 catalyst produced 1H-hyperpolarized hydrogenation products but their yields and 1H polarizations (P1H) were far from optimal. Finally, water-soluble analog of the Wilkinson's catalyst [Rh(P(p-C6H4SO3Na)3)3Cl] was identified as the best choice providing P1H of up to 3.3% for ethyl trimethyl ammonium and up to 10.9% for trimethyl propyl ammonium. The measured 14N T1 relaxation times of these reaction products at 7 T were  $3 \pm 1$  s and  $2.2 \pm 0.8$  s, respectively. To minimize the polarization losses due to efficient relaxation, high-field RF-based polarization transfer methods PH-INEPT and PH-INEPT+ [2] were employed for the polarization transfer from 1H to 14N nuclei in these compounds. Spin dynamics simulations provided the theoretical dependence of 14N NMR signal on the inter-pulse delays which was perfectly reproduced experimentally. The maximal 14N polarizations were 0.33% for ethyl trimethyl ammonium and 0.08% for trimethyl propyl ammonium salts polarized with PH-INEPT. Additionally, up to 0.14% 14N polarization was obtained for ethyl trimethyl ammonium bromide using PH-INEPT+ with continuous wave 1H decoupling. The obtained results demonstrate that hyperpolarization of quadrupolar nuclei in solution is

feasible despite the challenges.

This work was initiated in February 2020 and was supported by the Russian Science Foundation (grant 21-73-10105), Dr. Shchepin's startup grant (South Dakota School of Mines & Technology, USA), and Alexander von Humboldt Foundation.

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### CONTROL OF MAGNETO-OPTICAL PROPERTIES OF COBALT-LAYERS BY ADSORPTION OF A-HELICAL POLYALANINE SELF-ASSEMBLED MONOLAYERS

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Other hyperpolarization methods

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# Schematic representation of a self-assembled monolayer of helical molecules on a magnetic substrate (left) and the change of the magneto-optical response of the magnetic substrate after the adsorption of the helical peptides.

Recently, it was demonstrated that helical polyalanine molecules possess spin-polarising properties, allowing only electrons with a well-defined spin direction to be transmitted along the molecular chain, depending on the handedness of the molecule as well as on the direction of the electric field acting on the electron within the chiral molecule.[1] Various studies confirmed the spin-dependent properties using different experimental approaches. This phenomenon is called chirality-induced-spin-selectivity (CISS) and has already opened a new perspective for organic spintronic devices.[2] In addition to the CISS effect, it was recently reported that the adsorption of the pure enantiomers of  $\alpha$ -helical polyalanine (AHPA-L or AHPA-D) on a gold-covered ferromagnetic thin film could switch the out-of-plane magnetisation of the ferromagnetic thin film in a direction determined by the chiral nature of the enantiomer.[3] This effect was named as magnetism induced by the proximity of adsorbed chiral molecules (MIPAC). The same molecules were used to demonstrate the local magnetisation in gold-capped cobalt thin films by using the exchange interaction between the polyalanine molecules adsorbed on an atomic force microscopy (AFM) tip apex and the sample.[4] On the other hand, it was reported that the enantiomers of chiral molecules selectively chemisorb to an Au-capped ferromagnetic thin film substrate depending on the magnetisation, an effect which was further exploited to separate the enantiomers from their racemic mixture.[5] Thus, it is of utmost importance to understand the self-

assembling of chemisorbed helical molecules at the macro-scale (mm-range) and its influence on the magnetic properties of the substrate. In this work, we used spectroscopic ellipsometry in combination with magneto-optical Kerr effect spectroscopy and wide-field magneto-optical Kerr effect microscopy to provide the first magneto-optical experimental characterisation of  $\alpha$ -helix polyalanine-L (AHPA-L) SAMs on ferromagnetic thin films capped with a noble metal.[6]

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### DEVELOPMENT OF CANCER-TARGETED LIPOSOMES FOR 129XE HYPERCEST MRI

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Applications

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Cryptophane-A cages used for Xe hyperCEST are loaded into targeted liposomes

Cancers are the second most cause of death in Germany and among the most frequent causes of mortality worldwide. New ways to detect and treat cancers have been developed over the last decades. Nuclear magnetic resonance and MRI related techniques are used extensively for cancer diagnosis in clinical application. New approaches improving the selectivity and sensitivity are continuously evolving, particularly with the ongoing advancement of hyperpolarization (hp) techniques.

We expand the already proposed xenon biosensor concept that uses reversibly bound hyperpolarized 129Xe by introducing a liposomal nanocarrier platform [1]. We enable cancer cell specific targeting by providing reaction partners for a copper free click reaction between the nanocarrier and labeled cancer cells. Using the combination of 129Xe HyperCEST with liposomes takes advantage of the higher sensitivity of 129Xe HyperCEST when the host for reversible Xe binding engages in faster exchange kinetics in the lipid micro-environment.

We characterized the effects of the different components of the nanocarrier platform (POPC, cholesterol, cryptophane A-lipopeptide (Xe host for CEST)) via HyperCEST measurements and cell-based assays. The ratio of cryptophane-A to POPC strongly affects the CEST performance, with higher amounts of lipids causing an increase in the observed 129Xe CEST response from the lipopeptide and a quantified higher depolarization rate for on-resonant saturation. Increasing the fraction of cholesterol in the formulation decreases the observed 129Xe CEST effect, presumably due to membrane stiffening that impacts the exchange kinetics. Similar effects were already shown for loosely embedded CrA [2]. The analysis of the click reaction between azides on cells (or on synthetic beads as mockup targets) and the liposomes revealed challenges in synthesizing reactive liposomes and quantifying the reaction.

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### QUANTITATIVE 129XE HYPERCEST SPECTROSCOPY WITH COMPETITIVE GUESTS REVEALS IMPURITIES IN CUCURBIT[7]URIL

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**Applications** 

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The HyperCEST spectrum of Xe in a sample of dissolved CB7 has been analyzed under different competitive binding conditions.

HyperCEST MRI generates image contrast from chemical exchange saturation transfer with reversibly bound 129Xe. Commercially available cucurbit[n]urils are currently explored as HyperCEST agents [1–3] where the macrocyclic hosts with n = 6 or 7 (CB6/CB7) have been proposed as the most potent ones. Unfortunately, CB6 has poor water solubility unless Na+ ions are added but these decelerate the desired efficient exchange rate. CB7, however, comes with much better solubility and has been used in Xe HyperCEST designs.[4] A direct comparison of the CEST performance would give further insights into achievable detection limits. This prompted us to compare the HyperCEST signatures of both hosts in a study with detailed CEST analysis and selective competitive

displacement guests to reveal how easy the Xe exchange can be disturbed by other molecules with higher affinity.

NMR was performed at 9.4 T where hyperpolarization of 129Xe was achieved with a custom-built polarizer for SEOP using a gas mixture at 4.5 bar (abs.) with 5% Xe. HyperCEST spectra were obtained from commercially available CB7 and CB6 in the presence of the competitive guests cis-1,4-bis(aminomethyl)cyclohexane (1), cadaverine (2), and putrescine (3). Spectra were analyzed with exponential Lorentzian line shapes as predicted by the Full HyperCEST model (FHC).

The spectrum of dissolved CB7 material (50  $\mu$ M) shows a clear HyperCEST response at -95 ppm from free Xe in solution but it turned out that this is the identical chemical shift as in the spectrum of dissolved CB6. Moreover, addition of guest (1) that only fits into CB7 did not affect the signal at -95 ppm, whereas (2) and (3) completely suppressed this signal at a concentration far below the nominal CB7 concentration. This demonstrates that the signal is actually from CB6 rather than from CB7. We then performed a stepwise titration of (3) into the CB7 solution to quantify the amount of CB6. Overall, the quantitative HyperCEST analysis shows a consistent CB6 impurity of ca. 8% in CB7.

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### **Deniz Sezer**



### DYNAMIC VIEW OF THE SOLID-STATE DNP EFFECT IN SOLIDS AND LIQUIDS

RT 76

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#### A new DNP effect in viscous liquids

The solid-state effect of dynamic nuclear polarization (DNP) results from driving the zero-quantum and doublequantum (forbidden) transitions by off-resonance microwave irradiation. In the past, the effect of the microwaves in the solid effect has been modeled as a rate process, with the rate constants of the forbidden transitions calculated using first-order perturbation theory. By its very nature, this description considers only the populations of the relevant energy levels. In this talk, we present a non-perturbative treatment of the solid effect under continuous-wave excitation, which additionally accounts for the dynamics of all relevant coherences. Differently from the perturbative treatment, the developed dynamical description applies also at large microwave powers, when the Rabi nutation frequency is comparable to, or larger than, the nuclear Larmor frequency [1]. In addition, it is readily extendable to liquids, where the dipole-dipole interaction between the electronic and nuclear spins is randomly modulated by molecular diffusion [2]. In liquids, the theory predicts a new DNP effect, which is maximal at near-resonance irradiation (similar to the Overhauser effect) but is antisymmetric in the displacement from the resonance (like the solid effect). While the field profile of this new effect resembles thermal mixing, it is explained considering only one electronic spin and one nuclear spin. The predicted new effect, as well as the solid effect in liquids, agree quantitatively with recent high-field measurements of proton DNP from lipid bilayers at 320K [3].

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### QUANTIFICATION OF HYPERPOLARIZATION VIA HETERONUCLEAR FREQUENCY SHIFTS

**RT 77** 

Dissolution/Melt DNP

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Dynamic Nuclear Polarization (DNP) is a technique that utilizes a suitable radical and microwave irradiation to hyperpolarize nuclei in the sample, resulting in a significant enhancement of the NMR signal. However, polarimetry is challenging due to the requirement of comparison to the thermal equilibrium signal, which is accompanied by broad background signals and long buildup times in the solid state. A faster and potentially more reliable polarimetry method [1,4] would be to monitor frequency changes due to hyperpolarization rather than comparing signal strengths, which can be affected by a variety of circumstances. As one nuclear species is building up hyperpolarization, its magnetization slightly changes the local magnetic flux density in the sample [2]. This is sensed by nuclear spins, resulting in frequency shifts and changes in the NMR lineshapes [3,4]. We monitor these frequency shifts through parallel detection of protons and carbon spins during the DNP build-up. The observed spectral changes are compared against the expected effects predicted using numerical methods. We explore the viability of this method of polarimetry for different typical DNP sample compositions.

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### **KINETIC STUDY OF THE ACTION OF GLUCOSE-6-PHOSPHATE** DEHYDROGENASE ON HYPERPOLARIZED GLUCOSE-6-PHOSPHATE USING DISSOLUTION DYNAMIC NUCLEAR POLARIZATION (D-DNP)

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Applications, Dissolution/Melt DNP, Liquid DNP

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The metabolism of glucose is known to be disturbed in various pathological contexts, in particular in tumors, where cell proliferation is accompanied by an increase in glycolysis (Warburg effect). However, this deregulation also leads to an increased solicitation of the pentose phosphate pathway (PPP) activity leading through its oxidative stage to the production of NADPH, the main source of reducing power in the cell. The PPP plays a key role in the response to oxidative stress, one of the known factors involved in oncogenesis. Among the two enzymes that lead to the production of NADPH, Glucose-6-Phosphate dehydrogenase (G6PDH) and 6-Phosphogluconic dehydrogenase (6PGDH), we investigated the in-vitro kinetics of G6PDH using dissolution Dynamic Nuclear Polarization (D-DNP).[1] The sensitivity gain provided by this powerful technique allows one to observe the NMR signal of polarized species in an enzymatic reaction with sufficient signal-to-noise ratio with time resolution limited by the acquisition time (~ 500 ms), therefore compatible with near-physiological conditions.

To investigate the G6PDH, doubly labeled [13C, 2H]-G6P was enzymatically produced and purified through experiments used TEMPOL as the polarizing agent, and the use of cross-polarization sequences [2] yielded 13C polarization levels typically > 30% in the solid state, in fields of 6.7 T and 9.4 T and at a temperature of 1.2 K. DDNP experiments were then performed with various enzymatic activities and at different temperatures.

The observed reaction is deceptively simple. Indeed, the anomeric rearrangement of the G6P during the time of reaction cannot be neglected and must be considered in the analysis. Moreover, for higher enzyme activities, and at T=310 K, the isomerization of the reaction products was observed (delta/gamma phosphogluconolactone exchange), [3] which complexifies the extraction of model parameters even more. The conditions under which kinetic and relaxation parameters can be extracted from the simultaneous observation of G6P mutarotation and dehydrogenation will be discussed in detail. Finally, such methodological aspects as experimental optimization and reproducibility will be discussed.

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#### IMPORTANCE OF ORIENTATION CONTROL OF POLARIZING AGENTS IN TRIPLET DNP

General theory, General Instrumentation, Applications

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We have developed DNP using photo-excited triplet electrons (Triplet-DNP). The triplet electrons enable us to perform high temperature hyperpolarization, since they can be hyperpolarized through laser irradiation independent of magnetic field and temperature. In this talk, I will present the results of three samples with different orientation of polarizing agent.

1) conjugated molecule of polarizing agent and peptide in amorphous

A T1 of the matrix becomes the bottleneck of hyperpolarization especially at high temperature. The direct spin diffusion from the polarizing agent to the target without passing through the matrix can be realized when the polarizing agent is fixed close to the target region. Using 1 mM pentacene-p53 conjugate in 20:80 (v/v) D2O: DMSO-d6, the 1H polarization of 2.7% is observed at 0.67 T, 90 K.

2) single crystal doped with polarizing agent

The polarization of the triplet electrons depends on molecular orientation, and in the case of unoriented samples in amorphous matrix, they mostly cancel each other. In single crystal matrix, such as naphthalene, p-terphenyl, and picene, the polarization agents are oriented to maximize the polarization transfer efficiency. Using the samples, more than 30% of 1H polarization was achieved.

3) magnetically aligned polarizing agent in amorphous

Recently, we have also developed a method to orient only polarizing agents in amorphous using magnetically alignment materials.



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# PARAMAGNETIC METAL POLARIZING AGENTS FOR SITE-SPECIFIC DNP

RT 80

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Dynamic nuclear polarization (DNP) has shown tremendous potential to increase sensitivity in numerous MAS NMR applications [1]. Even though in conventional DNP experiments uniform signal enhancements are typically obtained, DNP itself can act as a source of specificity as well [2]. The hyperfine interaction is mediating the initial step of the complex mechanism of the overall DNP transfer. Therefore, the effects of the distance dependence of the dipolar hyperfine interaction between the electron spin (source) and nuclear spin (target) are of exceptional importance. By microwave irradiation, electron-nuclear coherences are generated which finally result in nuclear hyperpolarization. If subsequent spin diffusion is restricted, this transfer dynamic can act as a measure for hyperfine interaction gradient, theoretically leading to uniform, distance-independent DNP enhancement. Nevertheless, the direct-DNP build-up rate can act as a direct measure of this interaction and can thus yield distance information in biomolecules [4].

We present an approach to quantitatively investigate the distance dependence of DNP transfer based on paramagnetic metal complex polarizing such as Gd(III) complexes which are decorated with specifically isotopelabeled functional groups as molecular rulers. We show details about the chemical synthesis as well as EPR and NMR spectroscopic characterization. Computational methods for validation of distance distributions between source and target spin measured in DNP are also presented.

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#### CONTINUOUS REAL-TIME DETECTION OF HYPERPOLARIZED 1H AND **13C NUCLEAR SPINS IN LIQUIDS**

RT 81

General theory, General Instrumentation, PHIP, Dissolution/Melt DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation

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#### Example real-time magnetization evolution during hyperpolarization of 99% [1-13C]-fumarate in a microtesla field environment. (red = magnetic field during hyperpolarization, gray = background magnetic field applied along the Z axis, blue = difference

It is well appreciated that polarization transfer from electronic/atomic/molecular spin systems to nuclear spins offers to enormously enhance the utility of NMR and MRI, by thousand-fold enhancement of bulk 1H/13C/15N (... etc.) magnetic moments. It is lesser known is that, for similar reasons, electronic/atomic systems (e.g. alkali-atomvapor magnetometers) can additionally be utilized as efficient detectors of nuclear magnetization. Nowadays, alkalivapor magnetometers are inexpensive and easy-to-operate due to timely developments in medical fields such as magnetoencephalography and magnetocardiography [1]. The unprecedented sensitivity of alkali magnetometers in the sub-kHz band [2] and favorable environmental requirements, such as near-room-temperature operation, makes them highly useful to probe hyperpolarized NMR systems:

(1) We recently showed in [3] that a Rb-vapor magnetometer operating near zero field can be used to continuously track the magnetization of around 10%-polarized 13C spins in a dilute solution of the metabolic contrast agent [1-13C]-pyruvate (~0.08 M,1 mL, preparation: dissolution DNP). We will discuss details of how this continuous measurement is performed and how it can be used in robust quality-control procedures for in vivo administration of hyperpolarized compounds.

(2) We have also used Rb-vapor magnetometers to observe the real-time emergence of nuclear magnetization during conventional microtesla field cycling procedures. One example to be discussed is the [1-13C1]-fumarate system, which can be produced in the (nonmagnetic) proton singlet state by reacting [1-13C1]acetylene dicarboxylate with para-enriched H2 gas, and then hyperpolarized in a magnetic state by a 0-2  $\mu$ T field-sweep. We observe in real time the build-up of magnetization during the field sweep (see figure) for concentrations of [1-13C1]-fumarate on the order of 10 mM, where the internal field of the sample itself becomes similar in magnitude to the stray magnetic field from the applied field sweep (on the order of nT).

These specific systems as well as the procedures [3,4] for longitudinal detection will be discussed in detail.

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**RT 82** 

General theory, General Instrumentation, Applications, PHIP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation

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Schematic of an Earth's field NMR system with in-situ SABRE hyperpolarisation.

The portability and reduced cost of low-field (B0  $\leq$  2 T) NMR spectrometers provides potential to expand the range of NMR applications beyond the typical laboratory environment. However, low-field NMR detection suffers from reduced sensitivity. Parahydrogen (p-H2) induced polarisation (PHIP) methods are attractive for use with low-field NMR detection because they can generate orders of magnitude signal enhancement within seconds and require relatively simple and portable instrumentation.[1]

Signal enhancement in PHIP is achieved through a chemical reaction that breaks the symmetry of the protons in p-H2 that exist in a pure nuclear singlet spin state. This is achieved either through irreversible hydrogenation of an unsaturated precursor,[2] or via reversible binding of both p-H2 and substrate at a transition metal centre in the signal amplification by reversible exchange (SABRE) approach.[3] SABRE polarisation transfer is facilitated through the J-coupling network that exists within this transient intermediate complex and is optimised in a weak magnetic field of 0-10 mT. Experiments typically involve ex-situ polarisation transfer in a weak field, followed by transport of the sample into the NMR spectrometer for detection. This presents challenges for directly studying the SABRE polarisation transfer step and for the reproducibility of the SABRE response, due to the range of fields experienced by the sample during transport and variable sample transport times. An in-situ approach, where polarisation transfer and detection both occur in the same location, overcomes these challenges.

In this round-table presentation, the implementation of in-situ SABRE hyperpolarisation with low-field NMR

detection will be described. Field cycling coupled to Earth's field NMR and MRI detection [4] will be used to investigate the effects of p-H2 mixing on the observed SABRE signal and the lifetime of p-H2 in solution. In addition, we will discuss the practical implementation of in-situ p-H2 hyperpolarisation in a benchtop NMR spectrometer.

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#### EXPLORING THE SOLID-STATE-PHOTO-CIDNP EFFECT IN ARTIFICIAL POLY-L-PROLINE BASED, FLAVIN-AMINOACID DIADS

RT 83

CIDNP and ONP (incl NV centers)

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#### Mimicking nature with our polyproline based CIDNP-modelcompounds

Photo-CIDNP (photochemically induced dynamic nuclear polarization) is a remarkable phenomenon offering drastic signal-enhancements in nuclear magnetic resonance (NMR) spectroscopy. Upon blue light irradiation, spincorrelated radical pairs (SCRPs) are generated by electron transfer from an aromatic amino acid, to an excited electron acceptor dye such as flavin. The non-Boltzman distribution of spin-states in SCRPs leads to spin hyperpolarization. This effect is used by migratory birds as a spin-chemical compass and has the potential to be harnessed in medicinal applications for tissue imaging.[1] Photo-CIDNP experiments in a solvated environment are described by the radical-pair mechanism (RPM).[2] However, the mechanism for the photo-CIDNP effect in solid-state NMR remains subject of investigation, since in a solvent-free environment, SCRPs have no possibility of spatial diffusion.[3]

Together with our partners, we have a closer look at the origin of the solid-state photo-CIDNP effect within a molecular system. Here, the fine interplay of electronic and nuclear spins with regard to distance and spatial orientation of the donor-acceptor entities is currently investigated. Therefore, we create a toolbox of structurally different artificial diads based on conformationally rigid poly-L-proline. The electron donor and acceptor are attached to the polyproline type II helices either at the N- and C-terminus or directly to the proline core using click chemistry. The elaborated synthetic protocol relying on solid-state peptide chemistry allows for rapid and straightforward access to a plethora of different diads with a defined arrangement of the donor and acceptor moiety. This library of diads will be further investigated utilizing magic angle spinning (MAS) NMR techniques, as well as time-resolved CIDNP-NMR spectroscopy, to generate new knowledge in terms of spin-dynamics, structure-activity relationship and experimental setups of CIDNP-NMR spectroscopy.

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# MONITORING A PHASE TRANSITION OF CALCIUM PHOSPHATE BY DDNP NMR

RT 84

Dissolution/Melt DNP

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NMR plays an essential role in structure elucidation and reaction monitoring and has found wide application due to its versatility. Applications are not only limited to liquids, but also solid[1], and gases[2] can be analyzed through this method. However, mixtures of different phases, e.g., small particles in solutions, are not easily measurable due to the usually broad signals not being accessible through liquid phase NMR measurements. By dissolution dynamic nuclear polarization (dDNP)[3][4] and rapid substrate solidification, the two-phase system was yet made observable by liquid-state NMR. The presented methodology is demonstrated using calcium phosphate (CaP)[5] as a model system. Using "hyperpolarized" inorganic phosphate under fast precipitation conditions, we could follow the inclusion of the hyperpolarized phosphate ions into micrometer-sized particles within milliseconds. In both studied cases, the presence of broad signals superimposed by a narrow signal indicated the presence of solid CaP particles and solution state precursors simultaneously. The linewidth of the occurring liquid state precursor showed three times larger linewidths than free hyperpolarized phosphate. The conversion was slower or incomplete, depending on the availability of Ca2+ ions. The higher R1,eff of the liquid precursor was in stark contrast to the expected behavior of fast tumbling molecules. This indicates the conversion of the hyperpolarized SP into CaP during the detection period. SEM images obtained after the experiment further unveiled the presence of sCaP with particle sizes exceeding 10 um and explaining the solid-state type resonances. In conclusion, this approach enables the characterization of suspensions in equilibrium with their respective liquid-state precursor by hyperpolarized NMR on short time scales. Integrating molecular dynamics simulations and electron microscopy enabled the analysis of the recorded 1D NMR time series and gave insights into the material formation process[6].

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RT 85

General theory, Applications, PHIP, Optical pumping & SEOP, CIDNP and ONP (incl NV centers), Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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### First-principles calculation of spin interactions can provide the enhancement factors of gas-phase magnetometry.

Modern first-principles electronic structure theory can produce useful input to spin physics. I present a few studies related to spin-exchange optical polarisation (SEOP) processes and gas-phase (co)magnetometry, in which the relevant parameters have been obtained from calculations involving high-level electron correlation, basis-set limit and relativistic effects.

(1) Accurate interatomic potential energy and 129Xe hyperfine coupling curves, V(R) and A(R), for the 87Rb-129Xe system provide, via means of a virial expansion, a way of obtaining the EPR and NMR shifts and the 129Xe signal enhancement factor in SEOP polarisation [1].

(2) Corresponding calculations [2] for V(R) and the spin-spin coupling, J(R), curves for the 129Xe-3He system provide enhancement factor in excellent agreement with comagnetometer measurements [3], providing one of the first unequivocal demonstrations of spin-spin coupling over a van der Waals bond.

(3) In the case of 21Ne-3He system, the calculations can be taken to even higher level than in (2) rendering it possible to give very tight error margins to our computational prediction [4] of the enhancement factor for this system

- with experiments pending.

(4) Multiscale modelling involving molecular dynamics simulations, quantum-chemical calculations of the hyperfine couplings and coupled, incoherent electron-nucleus spin dynamics simulations reveal the role and details of spin transfer from 85/87Rb to 129Xe in van der Waals complexes in the SEOP cell [5]. In particular, the polarisation transfer happens in steps due to the modulation of the 129Xe hyperfine coupling with the van der Waals bond distance, whereas the 85/87Rb hyperfine coupling remains strong and limits the 129Xe polarisation build-up [6].

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#### RATE EQUATIONS IN HYPERPOLARIZED NMR

RT 86

General theory, Applications, CIDNP and ONP (incl NV centers), Triplet DNP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation, Other hyperpolarization methods

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### (a) Performance of the RF correction and build-up simulation of the rate equation model. (b) Sketch of the two compartment model

Despite tremendous efforts over the last decades, it is still very difficult to achieve experimental polarizations close to the theoretical maximum, e.g., the thermal electron polarization in DNP. We introduce a single compartment rateequation model to describe hyperpolarization methods from a macroscopic perspective with only a polarization injection and a relaxation-rate constant. This model sheds light on the relationship between the build-up time and steady-state polarization in terms of the injection and relaxation-rate constants. In addition, it allows the simulation of build-up dynamics based only on the theoretical maximum of the polarization, the measured build-up time and steady-state polarization (Fig. 1a). [1]

The RF pulses required to probe the hyperpolarization alter the characteristic time constants of the hyperpolarization process as well as the steady-state polarization. Correction for the impact of the RF pulses allows us to obtain accurate steady-state polarization, time constants and individual data points while applying flip angles up to 25° based on time-slicing simulations and experimental data acquired at 299 MHz (7 T) with 4-oxo-TEMPO in 1H glassy matrices between 2 and 4 K. (Fig. 1a). [1]

Owing to the ability to quantify the DNP injection and relaxation-rate constants of a given hyperpolarization buildup measurement, we found a much larger relaxation-rate constant during the polarization build-up than during the thermal decay. This additional relaxation shows a resonant microwave (MW) frequency-dependence and a MWpower scaling similar to the injection, explaining the identical polarization level for 15-65 mW power at the sample. Altogether, these results indicate that DNP under our conditions is limited by MW-induced relaxation as the measured thermal relaxation together with the MW-on injection-rate constant would allow nuclear polarization levels

around 60-70% (assuming an electron polarization of around 90% at 3.3 K, 7 T) in contrast to the experimentally measured 30-40%.

The model can be extended to two compartments by introducing an inter-compartment coupling constant (Fig. 1b). First results of this model will be discussed, in particular its application to the MW-on HypRes results from [2], showing a MW-power dependence of the intercompartment coupling and injection constants following the Torrey model of damped Rabi oscillations [3].

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A MOBILE 3D CELL CULTURE SYSTEM FOR LONGITUDINAL INTRACELLULAR METABOLIC PROFILING VIA HYPERPOLARIZED 13C-NMR

**RT 87** 

Dissolution/Melt DNP

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#### dDNP-NMR measured metabolic shift in etoposide treated HeLa cells.

Hyperpolarization with the dissolution dynamic nuclear polarization (dDNP) technique yields >10,000-fold signal increases for NMR-active nuclei (e.g. 13C). Hyperpolarized 13C-labeled metabolic markers thus allow real-time observations of biochemical pathways in living cellular systems, free from interfering background effects. This methodology enables the direct observation of altered intracellular reaction chemistry, such as those induced by drug treatment, infections, or other diseases. A reoccurring challenge for longitudinal cell studies of mammalian cells with NMR and dDNP-NMR is maintaining cell viability in the NMR spectrometer. The popularity of 3D cell culture methods is on the rise due to their ability to offer a more physiologically relevant environment in comparison to traditional 2D cell cultures. Based on such strategies, a mobile 3D culture system was devised. The clinical drug etoposide was used to treat cancer cells (HeLa) and the resulting change in metabolism was measured using hyperpolarized [1-13C]pyruvate. We show that sustaining the cell cultivation in cell incubators and only transferring the cells to the NMR spectrometer for the few minutes required for the dDNP-NMR measurements is an attractive alternative to cell maintenance in the NMR tube. High cell viability is sustained, and experimental throughput is many doubled.



#### PERDEUTERATED ALPHA-KETOGLUTARATE HYPERPOLARIZED BY RAPID SLIC-SABRE AT 50 T

**RT 88** 

PHIP, Transport of hyperpolarization, Loss of hyperpolarization & relaxation

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#### Polarization peak of deuterated alpha-ketoglutarate

#### INTRODUCTION:

Metabolic products of alpha-ketoglutarate (aKG) are strongly linked to glioma growth.[1,2] Signal amplification by reversible exchange (SABRE) is a promising low-cost, high-throughput hyperpolarization method and recently Adelabu et al. 13C-hyperpolarized (HP) aKG to 17.3% via SABRE in shield enables alignment transfer to heteronuclei (SABRE-SHEATH).[3,4] Recently, we have demonstrated SABRE using spin-lock induced crossing (SLIC) at 50  $\mu$ T to be efficient for HP of perdeuterated pyruvate, doubling the polarization levels due to favorable relaxation dynamics.[5] This achievement enabled the first in vivo metabolic imaging with purified SABRE HP [1-13C]Pyruvate-d3.[6] Here, we present our preliminary results investigating the hyperpolarization of aKG using SLIC-SABRE.

#### **METHODS:**

The samples were filled into standard 5-mm NMR tubes and contained 6 mM Iridum-based catalyst ([Ir(IMes)(COD)Cl]), 5 mM of Na2[3,3,4,4-d4]-aKG salt, 40 mM DMSO in methanol-d4. The solution was degassed by bubbling N2 for 1 min and the catalyst was activated with parahydrogen (pH2) for 2 min. The sample was placed in our SABRE polarizer comprising a 3-layer mu-metal shield and coils for static (B0) and radiofrequency magnetic fields (B1). For SHEATH, samples were bubbled with parahydrogen for 4 min at 10 °C and B0 = 0.42  $\mu$ T. For SLIC, we varied the temperature T (0.3 – 18 °C), B1 (1.425 to 2.375  $\mu$ T) and polarization build-up time t (60 – 300 s) while B0 was held at 50  $\mu$ T. HP 13C signals were detected and quantified using a 1T Benchtop NMR system.

#### **RESULTS:**

The 13C signal of HP [1-13C]aKG was detected at a chemical shift of 169 ppm. The highest 13C-hyperpolarization obtained with SLIC-SABRE was 10.5% at T = 10 °C, B1 = 1.9  $\mu$ T, and t = 60 s. Longer polarization build up did not improve this polarization. With SABRE-SHEATH we observed polarization levels up to 15.7 % for HP aKG using the optimized protocol of Adelabu et al.

#### DISCUSSION and CONCLUSION:

Here, SHEATH performed better than SLIC-SABRE for HP aKG. The short polarization build-up times indicate that T1 relaxation is dominant. Prolonging T1, e.g., using different sample compositions and reaction conditions seems promising to enhance polarization levels of this promising HP agent further.

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Liquid-state two-dimensional (2D) 13C-13C correlation NMR spectroscopy is a powerful method in the structural determination of organic molecules by directly probing the carbon connectivity. However, these methods require the presence of two neighboring 13C nuclei, often leading to low sensitivity. One promising strategy to improve the sensitivity of liquid-state 13C NMR is through Overhauser dynamic nuclear polarization (ODNP), whereby the polarization of a radical-centered electron spin is transferred to 13C nuclei of the target molecule through crossrelaxation during microwave irradiation. To date, several high-field liquid-state ODNP-NMR setups have been reported, allowing 10-100-fold enhancements of the signal intensity in one-dimensional pulse-acquire 13C experiments for small molecules compared with spectra acquired under thermal Boltzmann condition.[1] These results could help combine ODNP with more sophisticated techniques. Herein, we report examples of ODNPenhanced liquid-state 2D 13C-13C correlation NMR measurements at 9.4 T, enabled by a liquid-state ODNP-NMR setup. ODNP-enhanced 13C-13C correlation spectra can be performed using standard NMR pulse sequences on compounds with 13C-enrichment or natural 13C abundance upon applying continuous microwave irradiation to the sample. Compared to spectra recorded under Boltzmann conditions, the same set of diagonal and cross peaks are observed, with up to 30-fold enhancements in favorable cases. This corresponds to ~1000-fold reduction in experiment time for achieving a similar signal-to-noise. Additionally, we observed improved ODNP 13C enhancement of halogen-containing target molecules with stronger target-radical halogen bonding interactions. As revealed by density functional theory analyses, this is a result of enhanced target-radical hyperfine interaction, and such a correlation can be rationalized in the context of existing liquid-state ODNP theory. Combined, these results could bring new opportunities to ODNP-enhanced high-field liquid-state 13C NMR.

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#### IN VIVO DETECTION AND IMAGING OF AMINOPEPTIDASE ACTIVITY THROUGH THE RATIONAL DESIGN OF HYPERPOLARIZED MOLECULAR PROBES UTILIZING DISSOLUTION DYNAMIC NUCLEAR POLARIZATION.

**RT 90** 

Dissolution/Melt DNP

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#### The design of a dDNP-NMR molecular probe for detecting aminopeptidase N activity.

Dissolution Dynamic Nuclear Polarization (dDNP) is a hyperpolarization technique that can be applicable to a wide range of compounds, facilitating heightened sensitivity in Magnetic Resonance (MR) on a scale ranging from 10,000 to 100,000 [1]. [1-13C]Pyruvate, a representative dDNP-MR probe, has utility in clinical applications as a metabolic marker for certain tumors [2]. However, the number of practical dDNP-MR probes has been limited, hindering the observation of a variety of biological events. This limitation stems from the fact that most conventional in vivo-compatible dDNP-MR probes are derived from endogenous molecules [3], lacking an established methodology for designing dDNP-MR probes to detect new targets. In this context, the design of dDNP-MR probes for new biological phenomena has been highly demanded. Here, we present the development of dDNP-MR probes based on a rational design.

We have targeted aminopeptidases (APs) as the enzymes of interest, which specifically recognize and cleave the N-terminal residue of peptides or proteins. Notably, APN, which hydrolyzes N-terminal neutral residues such as alanine (Ala), serves as a significant biomarker because it is associated with tumor angiogenesis and metastasis [4]. Through computational analysis and enzymatic kinetic parameter measurements, we designed Ala-Gly-NMe2 as a molecular probe for APN activity, which exhibits highly selective and rapid hydrolysis by APN. Considering two

crucial magnetic parameters in the dDNP-MR field, namely, chemical shift change and spin-lattice relaxation time, we reached the final probe structure, Ala-[1-13C]Gly-d2-NMe2. The hyperpolarized probe was administered to xenograft mice (MIA PaCa-2) bearing tumors, followed by MR signal acquisition, successfully detecting and visualizing APN activity within the tumor region [5].

Ala-[1-13C]Gly-d2-NMe2 represents a well-designed probe that fulfills the requirements of dDNP-MR, including fast enzymatic reaction, large chemical shift change, long hyperpolarization lifetime, and other key characteristics. Based on this probe scaffold, we further developed dDNP-MR probes Xaa-[1-13C]Gly-d2-NMe2 to detect other aminopeptidases. Here in this talk, I will present these results, including the practical application of Ala-[1-13C]Gly-d2-NMe2.

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#### HYPERPOLARIZING DNA BY DISSOLUTION DNP

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Dissolution/Melt DNP

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Nuclear magnetic resonance (NMR) is a widely used technique, that can be employed to investigate various systems, ranging from small organic molecules to large macromolecular complexes. However, NMR suffers from an inherent drawback i.e. its sensitivity. A routine approach to overcome such boundaries is to enhance the signal intensity by scaling up the analyte concentrations or enriching the analyte with NMR active isotopes. These two solutions are not always feasible though. First, a high concentration can be either too cumbersome to achieve or even not desirable with respect to the designed experiment. Second, isotope enrichment typically leads to a dramatic increase in preparation costs and prevents the analysis of biologically relevant samples like blood plasma. Another approach emerging in the last few decades is to enhance the NMR signal via dynamic nuclear polarization (DNP). DNP exploits the possibility to transfer polarization from unpaired electron spins to nuclear spins [1]

Here we set to investigate a DNA hexamer, CACGTG, an enhancer box (E-box) [2]. E-box is recognized by the MYC oncoprotein and myc-associated factor X (MAX), two transcriptional factors that regulate a large number of genes. While NMR investigations of proteins are routinely done in either solution or solid phase, nucleic acid research presents a more challenging task. Therefore, we used dissolution DNP (DDNP) to enhance the NMR signal of DNA. We hyperpolarized water [3,4], which was then mixed with the E-box inside a 500 MHz NMR spectrometer to observe DNA protons, which exchange their polarization with the surrounding water. We explored a broad range of DNA concentrations in order to find solvent/DNA concentration ratios for optimal signal enhancement. Eventually, we achieved a 100-200 fold signal enhancement of protons adjacent to the rapidly exchanging phosphate moieties.

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#### HYPERPOLARIZING NUCLEAR SPINS USING PARAHYDROGEN AND METAL-FREE CATALYSTS: MF-PHIP

PHIP

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## The use of metal-free catalysts and parahydrogen leads to hyperpolarization of nuclear spins and NMR signal enhancements (MF-PHIP).

Parahydrogen-based nuclear spin hyperpolarization techniques support a growing range of NMR applications, including reaction monitoring, mechanistic elucidations, biomedical imaging, mixture analysis, etc. Chemical activation of parahydrogen molecules plays a key role in deriving enhanced NMR signals in these methods. Commonly, transition metal catalysts are employed to mediate such activations and produce hyperpolarized substances [1]. At the same time, more biogenic and sustainable main-group catalytic systems are known as metal-free activators for parahydrogen [2]. In this communication, we aim to provide an overview of the progress made in metal-free parahydrogen-induced polarization (MF-PHIP) and signal amplification by reversible exchange (MF-SABRE) based on the use of such metal-free catalytic systems.

We show that unimolecular pairs of sterically separated ('frustrated') Lewis acids and bases (FLPs) are promising metal-free parahydrogen activators that provide hyperpolarization of protons and heteronuclei (15N, 11B, 31P) of FLP-H2 adducts and free FLP molecules [2-4]. We also demonstrate that metal-free ansa-aminoborane FLPs catalyze hydrogenations of alkynes and imines, resulting in orders of magnitude signal enhancements at 9.4 T for alkene and amine products, respectively [5,6]. In addition to FLPs, pnictogen biradicals can lead to strong hyperpolarization effects in metal-free parahydrogen activations, enabling the formation of highly hyperpolarized adducts with parahydrogen [7]. We discuss the role of kinetic parameters, dihydrogen bonding and structural features in relation to the observed hyperpolarization effects, providing a perspective for the use of these systems in NMR applications.

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#### DYNAMIC NUCLEAR POLARIZATION OF INORGANIC HALIDE PEROVSKITES

**RT 93** 

DNP

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Dynamic nuclear polarization (DNP) under magic angle spinning (MAS) has shown tremendous potential to overcome the sensitivity limitations of MAS NMR, enabling the acquisition of highly selective and sensitive NMR spectra. However, so far, DNP methods have not been explored in the context of inorganic lead halide perovskites, which are a leading class of semiconductor materials for optoelectronic applications. Here, I will show how we can study cesium lead chloride using MAS DNP, and quantitatively compare DNP methods based on impregnation with a solution of organic biradicals with doping of high-spin metal ions (Mn<sup>2+</sup>) into the perovskite structure [1]. We find that metal-ion DNP provides the highest bulk sensitivity in this case, while highly surface-selective NMR spectra can be acquired using impregnation DNP. The performance of both methods is explained in terms of the relaxation times, particle size, dopant concentration, and surface wettability. We envisage the future use of DNP NMR approaches in establishing structure-activity relationships in inorganic perovskites, especially for mass-limited

samples such as thin films.

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