

ICOMIS4 2022

Intercontinental Magnetic Resonance Conference on Methods and Applications

February 9-11, 2022

Time: 12:00-15:00 (Berlin/Paris, CEST)

Organised by:

Daniel Abergel, Gerd Buntkowsky, P. K. Madhu



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Foreword

ICONS4-2022 is the fourth edition of the on-line magnetic resonance conference on methods and applications. ICONS aims to cover recent topics in both NMR and EPR. The meeting is an off-shoot of the Intercontinental NMR Seminar Series that started on April 8, 2020. This seminar series enables communication and dissemination of research ideas among the magnetic research community especially in the times of the COVID-19 pandemic. The seminar series also gives early-stage researchers an opportunity to give seminar talks and interact with colleagues from different countries. The success of the seminar series prompted us to introduce ICONS conference series to highlight the recent research contributions from some of the leading groups in magnetic resonance. We target to reach a good cross-section of the community even despite the time-zone disparity. We sincerely hope that both the seminar series and the conference will prove to be beneficial to the magnetic resonance community and contribute to the growth of magnetic resonance science and help many of us to stay connected. The ICONS4-2022 will focus on solution-state NMR and hyperpolarisation methods.

Daniel Abergel

Gerd Buntkowsky

P. K. Madhu

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Time/Paris/UTC	February 9 Wednesday	February 10 Thursday	February 11 Friday
12:00-12:45 11:00-11:45	Ardenkjær- Larsen	Kupče	Degen
12:45-13:30 11:45-12:30	Nacher	Frydman	Leskes
13:30-14:15 12:30-13:15	Cavallari	Kuchel	Duckett
14:15-15:00 13:15-14:00	Meersmann	Cavagnero	De Paëpe

Hyperpolarized MR: Clinical translation of dissolution-DNP

Jan Ardenkjær-Larsen

Technical University of Denmark, Department of Health Technology

Hyperpolarized Magnetic Resonance is a new medical imaging modality that enables exceptional possibilities in studying changes in metabolism of tissue and organs in vivo in real-time¹. The method is enabled by a more than 10,000-fold enhancement² of the signal from metabolic contrast agents that probe central metabolic pathways. The contrast agent is typically enriched in ¹³C and polarized by dissolution Dynamic Nuclear Polarization (dDNP). The contrast agent circulates via the vasculature to the tissue of interest, where it is taken up by the tissue cells and metabolized into specific products. MR is unique in several ways: 1) it already provides anatomical and morphological images with high resolution and contrast based on the tissue water protons, 2) it does not expose the patient to any ionizing radiation, and 3) it is a spectroscopic method that allows quantification of the individual metabolites. The first hyperpolarized contrast agent used in humans³⁻⁶ is ¹³C-pyruvate. Pyruvate is at a pivotal point in glycolysis and allows us to directly probe the Warburg effect through the elevated lactate-to-pyruvate ratio. The hope is that more accurate diagnosis and staging can be made, and that the method will provide an early read-out of response to treatment, and the first human studies are encouraging.

In this talk, we will present recent polarizer developments⁷ targeting clinical translation. Clinical use of hyperpolarization requires reliable and automated equipment with high efficiency. We discuss new conceptual ideas on the dissolution system (fluid path) that improves practical use, reduces running costs, and ensure sterility with high polarization.

We will also discuss developments in receiver technology for hyperpolarized ¹³C metabolic imaging. Tight-fit, blanket coils⁸ with sensitivity mapping through ²³Na are demonstrated providing a path to parallel imaging for hyperpolarized MR.

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February 9, 12:45-13:30 (Paris/German)

Polarised noble gases: hyperpolarisation methods and applications

Pierre Jean-Nacher

ENS Paris, France

I will present a brief review of the currently used optical pumping (OP) -based methods used to obtain near-unity nuclear polarisation in Xe129 and He3 gases, and will briefly report on progress of OP-free polarisation of He3 in a magnetised plasma. Selected applications of polarised noble gases to magnetometry, high-energy and neutron physics, and biomedical imaging will illustrate the wide range of their uses.

ParaHydrogen-based hyperpolarized metabolites for magnetic resonance

Eleonora Cavallari

Department of Molecular Biotechnologies and Health Sciences, University of Torino, Torino, Italy

One of the most promising approaches for overcoming the fundamental sensitivity limit of magnetic resonance (MR) for metabolical in vivo applications is to increase the spin polarization of MR probes. This already allowed completely new applications of MR by injecting exogenous MR probes that have been prepared by hyperpolarization (HP). Natural metabolites can be hyperpolarized and injected, allowing the metabolism to be imaged in the human body, with high clinical potential [1]. Hyperpolarization is a transient property but its duration is enough to follow the metabolic fluxes and transformation, observing the dynamic labelling in tissues.

The primary existing method for generating HP molecules in solution is the dissolution-Dynamic Nuclear Polarization (d-DNP). It is a very demanding technology involving cryogenics, high magnetic fields and high-frequency microwaves. The technology requires a high level of technical skills and is very expensive. In addition, it takes a long time (>30 min) to generate the HP probe, and most importantly the method only works in batch mode, making a continuous generation of HP solution impossible.

An alternative hyperpolarization method exists, based on the para-isomer form of hydrogen gas, the parahydrogen (pH₂) [2]. Potentially, ParaHydrogen-based approaches can provide a cheap and versatile solution to achieve nuclear hyperpolarization. The method requires specifically-designed molecules precursors (in case of pH₂ induced polarization application) [3], a carefully timed and optimised combination of chemical processes, hydrodynamic liquid transfers, magnetic field manipulations and occasionally phase separations.

In recent years, sufficiently high polarization levels were observed for several metabolites [4], such as fumarate [5] and pyruvate [6], and much attention has also been devoted to the improvement of the biocompatibility of the hyperpolarized product, in particular in terms of removal of toxic solvents, catalyst and other chemicals generated in the process.

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Hyperpolarized noble gas MRI in health care and chemical engineering

Thomas Meersmann

Sir Peter Mansfield Imaging Centre, School of Medicine, University of Nottingham, UK, School for Electric and Electronic Engineering Ningbo, China

Pulmonary MRI with hyperpolarized (HP) noble gases enables functional and microstructural MRI of lungs in health and disease. These contrast agents are most commonly generated through spin exchange optical pumping (SEOP) with high power diode array lasers. For example, SEOP typically enhances the ^{129}Xe signal, observed in clinical MRI scanners (i.e. at 1.5 – 3 Tesla) by 4 – 5 orders of magnitude compared to the thermal equilibrium signal. Therefore, SEOP can produce hp ^{129}Xe as MRI contrast agent for the gas phase and tissue dissolved phase [1]. In addition, our group has introduced hyperpolarized nuclear spin $I = 9/2$ noble gas isotope ^{83}Kr as a new MRI contrast agent to probe surface volume ratios in lungs and materials. The surface quadrupolar relaxation (SQUARE) of ^{83}Kr is a potential biomarker for emphysema as demonstrated through SQUARE T_1 maps in excised lungs of rodent model (Fig. 1) [2].

Similarly, the gaseous MRI contrast agent HP ^{129}Xe can also be applied to establish the structure-transport relationship in chemical engineering and related fields [3, 4]. For example, gas transport and reactive zones in diesel catalysts, that consist of hierarchical porous solids with ordered and disordered levels in the hierarchy, can be explored (Fig. 2). Vice versa, the engineering work impacts health care technology, and molecular hydrogen used as buffer gas during SEOP can be removed through catalytic

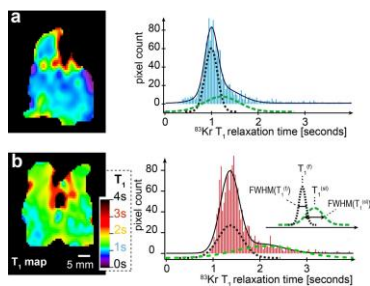


Figure 1: (a) Hp ^{83}Kr SQUARE T_1 map of control lung and (b) of emphysema model lung. The frequency of the T_1 – i.e. the pixel (voxel) count with a particular T_1 value – is shown in the histograms next to the SQUARE maps indicate a clear shift of the T_1 relaxation times in the disease model towards longer times. The insert shows the four parameters that can be extracted from bimodal Gaussian fitting of the histograms.

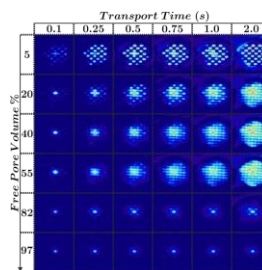


Figure 2: Two-dimensional spin density images of the spatial dispersion of hp ^{129}Xe , within a radial cross-section of a combined selective catalytic reduction (SCR) filtration monolith, with increasing transport time. High gas density is indicated by red colors, and lower densities are indicated by yellow to blue colors.

combustion [5]. Remarkably, the very low spin temperature of < 0.1 K of the hyperpolarized state, survives the high reaction temperature (> 1500 K) and the concept is being applied for the purification of hyperpolarized noble gas contrast agents.

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Design of NMR supersequences for small molecule applications

Ēriks Kupče

Bruker UK Ltd., Coventry, CV4 9GH, UK

Structure elucidation and characterization of small molecules by NMR largely follows well-established protocols that rely on a core set of 2D correlation experiments such as COSY, TOCSY, NOESY, ROESY, HSQC, HMBC, ADEQUATE or INADEQUATE. We show that up to 10 such experiments can be combined into a single entity called supersequence [1,2]. This leads to a dramatic reduction of data collection time and significant improvements in sensitivity of NMR measurements. Such supersequences can be tailored for specific applications, for instance, the analysis and characterization of molecular structure of complex organic molecules. When combined with computer assisted structure elucidation (CASE) software such as CASPER, structure of oligosaccharides can be established from a single measurement with a high degree of confidence. Likewise, 2D NMR-based metabolomics with sensitivity improved versions of HSQC/TOCSY NOAH supersequences allow efficient measurement of multiple 2D NMR spectra (HSQCsi and/or HSQCsi-TOCSY and TOCSY) of metabolomics samples in a single experiment for the accurate and comprehensive identification and quantitation of metabolites. Involving multiple receiver technology opens new avenues for multiplexing NMR experiments thus reducing the cost of NMR analysis, increasing sensitivity and the information content of NMR measurements [3,4]. Here we discuss the design principles of such super sequences.

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Sensitivity-enhanced bioliquids and solid state NMR: Exploiting the media

Lucio Frydman

Department of Chemical and Biological Physics, Weizmann Institute, Israel

Chemical exchange saturation transfer, or CEST, is a central tool in modern metabolic imaging. CEST exploits the fast exchanges that labile hydrogens undergo with water in order to amplify the signatures of hard-to-observe metabolites. At the same time, it has often been assumed that fast exchanges with the solvent complicate or altogether preclude the observation of the labile sites. In the present study we discuss how exchanges with the medium can actually be put to good use in order to enhance certain valuable molecular signatures –particularly those involving NOE and TOCSY correlations between labile and non-labile protons in biomolecules. Using relatively simple manipulations tunable by straightforward calibrations, it is shown that solvent exchanges can be used to amplify imino, amino, amide and hydroxy peaks in the 2D NOESY/TOCSY NMR spectra of nucleic acids, proteins and saccharides, by factors ranging from 2 to 10-fold. Even larger gains in sensitivity per unit time –up to two orders of magnitude– can be attained when the spectra are sparse, in which case the information can be efficiently encoded via selective manipulations. Heteronuclear information can also be incorporated into this kind of experiments, leading to high resolution and enhanced sensitivity, in minimal acquisition times. In fact chemical exchanges are not the sole mechanism capable of amplifying NMR spectra in such manner: also spin-diffusion effects among abundant spins, can be used to a similar end when trying to sensitize the spectra of dilute, insensitive species. The talk will conclude with a demonstration of how this can be brought to bear in order to impart high sensitivity/unit_time gains in wide-line solid state NMR of ^{14}N , ^{17}O , ^{33}S and other “tough” nuclides, by exploiting mostly unused polarization in the surrounding media.

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February 10, 13:30-14:15 ((Paris/German)

Dissolution dynamic nuclear polarization of $^{133}\text{Cs}^+$ to study its transmembrane exchange in cells

Philip W. Kuchel

University of Sydney, Sydney, NSW, Australia

The first report, on the application to mammalian cells, of ^{133}Cs dissolution dynamic nuclear polarization (^{133}Cs -dDNP) NMR spectroscopy was with $^{133}\text{Cs}^+$ in suspensions of human erythrocytes (red blood cells; RBCs) [1]. This NMR based analysis quantified membrane transport kinetics on the sub-10-second time scale. Key technical developments were made to obtain reproducible sample delivery and thus obtain high quality NMR spectra, every second. The rate of the membrane transport was enhanced by using a cation-free medium together with Yoda1 which is an activator of the mechanosensitive cation channel Piezo1, through which Cs^+ passes.

First-order rate constants that describe the transmembrane flux were estimated using statistical methods in Mathematica. Estimates of fluxes were in the range 4-70 $\mu\text{mol Cs}^+(\text{L RBC})^{-1}\text{s}^{-1}$. These rates are slower than for urea [2] but they are comparable to those of glucose [3].

The methodology and analytical procedures should be applicable to studying transmembrane cation transport in other cellular systems, and potentially in vivo. Various challenges will be discussed.

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Nuclear-spin hyperpolarization of amino acids and proteins in solution via LC-photo-CIDNP

Silvia Cavagnero^{1*}, Hanming Yang¹, Clayton A. Mickles¹, Kenji Sugisaki²

¹University of Wisconsin, Madison (USA)

²Osaka City University, Osaka (Japan)

Low-concentration photochemically induced dynamic nuclear polarization (LC-photo-CIDNP) has emerged as an effective tool for the hyperpolarization of aromatic amino acids in solution, both in isolation and within proteins. In this talk, we will present the basic aspects of this LED-enhanced NMR technology, including recent advances that further increase its capabilities. For instance, the presence of low- μM concentrations of the reductive radical quencher vitamin C (VC, i.e., ascorbic acid) enables LC-photo-CIDNP data acquisition for a significantly longer time than ever possible before [1]. This approach further enhances the sensitivity of LC-photo-CIDNP for proteins in solution by more than 100%. Larger enhancement factors are achieved in experiments involving more transients [1]. Second, theory predicts that the coupling of an electron spin to multiple nuclei has adverse effects on nuclear-spin hyperpolarization. Thus, we synthesized the selectively labeled Trp isotopolog α -¹³C- β , β ,4,5,6,7-d₆-Trp that replaces uniformly ¹³C,¹⁵N labeled Trp via a synthetic route previously developed in our group [2]. This isotopolog displays unprecedented LC-photo-CIDNP enhancement. Conveniently, the combination of the two above advances leads to additional increases in NMR sensitivity in liquids, enabling NMR data collection in the low nM range in less than a minute at 600 MHz. Finally, we will show that the LC-photo-CIDNP technology works well even in highly complex media, including cell-like *milieux*. This advantage suggests future applications to solve *in situ* biological questions that require low sample concentrations.

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February 11, 12:00-12:45 (Paris/German)

Towards a single-molecule NMR platform in diamond

Chistiran Degen

ETH Zurich, Switzerland

Isolated spin defects in diamond have become an exciting playground for NMR and EPR experiments, because optical detection allows measuring them at the single-spin level. One of these defects, the nitrogen-vacancy center, preserves its excellent longitudinal and transverse relaxation times up to room temperature. Our group is harnessing the properties of NV centers for a variety of high-resolution magnetic sensing applications.

In this talk, I will discuss our efforts in utilizing NV centers for detecting single nuclear spins in their vicinity, so as to perform atomic scale mapping of nuclei with three-dimensional spatial resolution. In a first part of the talk, I will focus on detection of “internal” carbon-13 spins as a testbed for 3D atomic imaging. In a second part, I will outline the challenges and initial efforts in translating these methods for detecting nuclear spins in “outside” molecules, including generation of near surface (<5 nm) NV centers, chemical functionalization of the diamond surface, and detection of NMR signals from outside ^1H and ^{19}F nuclei. A far goal of this project is to realize a single-molecule NMR technique that can image the structure and follow dynamics at the single-molecule level.

February 11, 12:45-13:30 (Paris/German)

Paramagnetic metal ions DNP for bulk and surface sensitivity in inorganic solids

Michal Leskes

*Department of Molecular Chemistry and Materials Science, Weizmann Institute of Science,
Rehovot, Israel*

Paramagnetic metal ions provide an efficient route for nuclear hyperpolarization in the bulk of inorganic solids.[1] In this talk I will describe recent developments of this approach, the conditions and mechanisms for gaining high sensitivity as well as some of the applications of metal ions DNP to gain structural insight into energy storage and conversion materials.

A key advantage of the approach is the ability to efficiently polarize low gamma and/or low abundance nuclei directly from the metal ion dopant with uniform polarization across the crystal.[2] This enables detection of 2D homonuclear correlations of extremely low sensitivity nuclei such as ^{89}Y , which provide medium range structural insight into oxygen vacancies distribution, a critical parameter in the design of solid electrolytes with high oxygen ion conductivity.[3] Furthermore, direct polarization from metal ions in the bulk extends to the material interface. I will show how the combination of endogenous interfacial polarization, from the bulk of the material, with exogenous polarization, from biradicals, emerges as a powerful structural tool for thin coatings and buried solid interphases.[4] Finally, I will present some of our ongoing efforts to characterize the paramagnetic dopants through their effect on nuclear relaxation times and how this effect is related to measured DNP enhancements.[5]

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Using hyperpolarisation delivered through SABRE to probe reactivity

Simon B. Duckett, Peter J. Rayner, Marianna Fekete, Callum A. Gator, Norman Turner, Aneurin J. Kennerly,

University of York, UK

Positron emission tomography is a very sensitive technique that images changes in metabolic processes, blood flow and agent absorption in the body. It takes long-lived radionuclides and embeds them into suitable receptors to create the radiopharmaceuticals that convey diagnostic responses. Unfortunately, this process can be complex and costly. Magnetic resonance imaging (MRI) is another powerful diagnostic method, but inherent low sensitivity means without hyperpolarisation routine clinical measurements probe highly abundant water.

One method to create hyperpolarization involves para-hydrogen ($p\text{-H}_2$) induced polarization (PHIP), which despite being discovered in the 1980's, is only now receiving world-wide attention. Two recent PHIP advances that utilize $p\text{-H}_2$ are exemplified by Signal Amplification by Reversible Exchange (SABRE)¹ and $p\text{-H}_2$ induced polarization with side-arm hydrolysis (PHIP-SAH).² As $p\text{-H}_2$ can be prepared to a level of 50% purity by simply cooling H_2 gas by liquid nitrogen,⁵ one could imagine the wide spread future use of this sensitisation approach.

Here, we demonstrate how it is possible to turn PHIP into a versatile tool for the *in situ* synthesis of long-lived and highly MR visible precursors, akin to the radionuclides of PET. These reactive precursors are rapidly embedded into important molecular reporters to illustrate the creation of the hyperpharmaceutical. By using this approach to monitor reactivity, we demonstrate the detection of previously unseen reaction intermediates.

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Improved polarizing agents and cost-effective sustainable cryogenic helium MAS for high field dynamic nuclear polarization

Gaël De Paëpe

Univ. Grenoble. Alpes, CEA, IRIG, MEM, 38000 Grenoble, France

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 ^{13}C - ^{15}N - ^{13}C correlation experiments** that can be used for crystal structure determination of **small molecules** and to study **disease-relevant protein aggregates** and **ligand arrangement and proximities at the surface of nanocrystals**.**[1,2,3]** 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). This currently impedes the application of the technique to a wider range of systems (e.g., protonated solids, systems with short ^1H T₁, etc.), as well as non-receptive nuclei at natural isotopic abundance (e.g., ^{17}O , ^{43}Ca , etc.). There is thus a need to develop new approaches to increase DNP-NMR sensitivity by several orders of magnitude.

I will first highlight our effort towards developing **new polarizing agents guided by MAS-DNP simulations**. The potential of these simulations combined with DFT calculations and high-field EPR to qualitatively and quantitatively predict hyperpolarization efficiency of particular PAs will be discussed and a family of radicals (AsymPol) will be introduced.**[4,5]** The performance of new members of the AsymPol family will be discussed (**cAsymPol-POK, AsymPol-TEK, cAsymPol-TEK**) highlighting their excellent performance at high field, fast MAS, especially when **targeting protonated matrix with short ^1H bulk T_{1n}**.**[6]**

In a second part, I will also discuss the Grenoble approach towards sustainable ultra-low temperature NMR and DNP.**[7]** It relies on the use of a **closed loop He cycle to spin and cool the sample**. Using a first generation He DNP probe, we were able to report **faster sample spinning** and **one to two orders of magnitude of additional timesaving compared to 100 K DNP experiments**.**[7]** Nevertheless, this first-generation probe was too lossy to work sustainably with a single cryo-cooler. For this reason, we developed a second generation He DNP probe with an improved design while maintaining sample insert/eject as well as robust tuning/matching capabilities (*Coll.* Bruker). The setup we have developed over the years relies on the use of a **single compressor for Bearing/Drive/VT** and can reach **35 K at the sample** while using **only a single two-stage cry-cooler** for the three lines. The **sample can be changed in minutes using an innovative insert/eject system** that prevents moisture to enter the system. ^1H decoupling of 100 kHz (64W) can be applied during 25 ms without arcing. Finally, we compared **the sensitivity returned with our home-made 3.2 mm ULT DNP probe at 40 K and a commercial Bruker 3.2 mm LT DNP probe at 100 K using cAsymPol-POK (one of the best PA currently available) demonstrating one to two orders of magnitude of additional time-savings on microcrystalline solids**.**[8]**

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