HYP18
HYPERPOLARIZED MAGNETIC RESONANCE

2-5 September 2018
Grand Harbour Hotel
Southampton, UK
hyp18.com

CONFERENCE PROGRAM
Sponsors

The organisers thank the following sponsors for their support:
The Groupement AMPERE (Atomes et Molécules Par Études Radio-Electriques) is an association of scientists active in the fields of Magnetic Resonances, Optics, Dielectrics, Magnetic Resonance Imaging, as well as in the development of the related methodologies and technologies. Although the roots and the basic activities are in Europe, members are from all over the world.

Today it is the largest organization in Europe dedicated to promoting Magnetic Resonance in Physics, Chemistry and related fields.

HYP18 is an activity of the Hyperpolarized Magnetic Resonance division of AMPERE, chaired by Geoffrey Bodenhausen.

https://www.ampere-society.org/
Welcome

…to HYP18, Southampton, UK. This conference will cover the main areas of nuclear hyperpolarization and some other methods for sensitivity enhancement in NMR and MRI, including:

- several variants of dynamic nuclear polarization (DNP)
- optical pumping
- quantum-rotor-induced polarization
- parahydrogen-induced polarization
- diamond magnetometry

and key applications such as clinical imaging, materials science, and molecular structure determination.

HYP18 follows on from a series of conferences on DNP:

- Nottingham, UK (2007)
- Königstein, Germany (2009)
- Lausanne, Switzerland (2011)
- Copenhagen, Denmark (2013)

HYP18 has a broader scope and intends to promote interactions and synergies between the full range of hyperpolarization technologies.

Malcolm H. Levitt (Chair)
Giuseppe Pileio (Local Organiser)
COMMITTEES

Scientific Committee
- Malcolm Levitt, Southampton, UK (Chair)
- Jan Henrik Ardenkjaer-Larsen, Copenhagen, Denmark
- Marc Baldus, Utrecht, The Netherlands
- John Blanchard, Mainz, Germany
- Konstantin Ivanov, Novosibirsk, Russia
- Thomas Meersman, Nottingham, UK

Local Organisers
- Giuseppe Pileio, Southampton, UK
- Malcolm Levitt, Southampton, UK

Administrative Support
- Hannah Duncan
- Kat Cutler

Volunteers
- Stuart J. Elliott
- Karel Kouril
- Hana Kourilova
- James Eills
- Christian Bengs
- Francesco Giustiniano
- Maria Concistrè
- Manvendra Sharma
- George R. Bacanu
- Julia Hollenbach
- Mohamed Sabba

many thanks to all!
Conference Venue

Grand Harbour Hotel
West Quay Road
Southampton SO15 1AG
Tel: 023 8063 3033
E-mail: info@grandharbourhotel.co.uk

location: https://goo.gl/maps/hJCPiCXa8vs

university (Highfield campus)

train station

venue

ferries to Isle of Wight
FLOORPLAN (GROUND FLOOR)
FLOORPLAN (FIRST FLOOR)
PROGRAM AT A GLANCE

<table>
<thead>
<tr>
<th>Time</th>
<th>Session 2</th>
<th>Session 6</th>
<th>Session 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-</td>
<td>Coffee</td>
<td>Coffee</td>
<td>Coffee</td>
</tr>
<tr>
<td>11-</td>
<td>Session 3</td>
<td>Session 7</td>
<td>Session 11</td>
</tr>
<tr>
<td>12-</td>
<td>Lunch</td>
<td>Lunch</td>
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</tr>
<tr>
<td>13-</td>
<td>Session 4</td>
<td>Session 8</td>
<td>Session 12</td>
</tr>
<tr>
<td>14-</td>
<td>Tea and Posters</td>
<td>Tea and Posters</td>
<td>Tea and Posters</td>
</tr>
<tr>
<td>15-</td>
<td>Opening</td>
<td>Session 9</td>
<td>Session 13</td>
</tr>
<tr>
<td>16-</td>
<td>Session 1</td>
<td>Session 5</td>
<td>Session 13</td>
</tr>
<tr>
<td>17-</td>
<td>Drinks</td>
<td>Drinks</td>
<td>Drinks</td>
</tr>
<tr>
<td>18-</td>
<td>Dinner</td>
<td>Dinner</td>
<td>Dinner</td>
</tr>
<tr>
<td>19-</td>
<td>Drinks</td>
<td>Drinks</td>
<td>Social Dinner</td>
</tr>
<tr>
<td>20-</td>
<td>Dinner</td>
<td>Dinner</td>
<td>Social Dinner</td>
</tr>
<tr>
<td>21-</td>
<td>Perspective Talk</td>
<td>Dinner</td>
<td>Social Dinner</td>
</tr>
<tr>
<td>22-</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Detailed Program**

A pdf of all talk and poster abstracts is available at [hyp18.com](hyp18.com)  
Codes Sn, Mn, Tn, Wn below refer to Sunday, Monday, Tuesday, Wednesday talks. ⇒ Pn denotes a cross-reference to a poster.

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:00–16:00</td>
<td>REGISTRATION</td>
</tr>
<tr>
<td>16:00–16:25</td>
<td>Opening Remarks: Malcolm Levitt</td>
</tr>
</tbody>
</table>
| 16:25–17:10    | Chair: Geoffrey Bodenhausen (ENS Paris, FR)  
|                | John Kurhanewicz (University of San Francisco, US) Hyperpolarized $^{13}$C MRI: Initial clinical applications |
| 17:10–17:30    | S2⇒P5  
|                | Mor Mishkovsky (EPFL, CH) Direct detection of glucose metabolism in vivo in human GBM mice models by hyperpolarized $[^2H_7,^{13}C_6]$–glucose |
| 17:30–17:50    | S3⇒P82  
|                | Eleonora Cavallari (University of Turin, IT) First in cellulo and in vivo metabolic studies using parahydrogen–hyperpolarized $[1–^{13}C]$–pyruvate |
| 17:50–18:25    | Mathilde Lerche (DTU, Copenhagen, DK) Metabolic signatures of living cells |
| 19:30–21:00    | DINNER        |
| 21:00–21:35    | S5  
<p>|                | Kevin Brindle (University of Cambridge, UK) Metabolic imaging with hyperpolarized $^{13}$C–labelled cell substrates – from mouse to man |</p>
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00–9:45</td>
<td>M1</td>
<td>Thomas Theis (Duke University, US)</td>
<td>SABRE of X-nuclei: from basic spin physics to future biosensing applications</td>
</tr>
<tr>
<td>9:45–10:05</td>
<td>M2</td>
<td>Stefan Glöggler (MPI Göttingen, US)</td>
<td>Parahydrogen Induced Polarization: over 50% $^1$H and $^{13}$C polarization of metabolite precursors and 12% $^{15}$N polarization with 20 minutes $T_1$ in water</td>
</tr>
<tr>
<td>10:05–10:25</td>
<td>M3</td>
<td>Alexandra Yurkovskaya (ITC Novosibirsk, RU)</td>
<td>Light-induced hyperpolarization in reversible reactions of biomolecules</td>
</tr>
<tr>
<td>10:25–11:00</td>
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<td>COFFEE</td>
</tr>
<tr>
<td>11:00–11:20</td>
<td>M4</td>
<td>Danila Barskiy (UC Berkeley, US)</td>
<td>Metal–Free parahydrogen–based hyperpolarized contrast agents produced via rapid catalyst capture</td>
</tr>
<tr>
<td>11:20–11:40</td>
<td>M5</td>
<td>James Eills (University of Southampton, UK)</td>
<td>Field–swept polarization transfer in parahydrogen NMR</td>
</tr>
<tr>
<td>11:40–12:15</td>
<td>M6</td>
<td>Meghan Halse (University of York, UK)</td>
<td>$^1$H and $^{13}$C benchtop NMR spectroscopy with SABRE hyperpolarisation</td>
</tr>
<tr>
<td>12:15–13:45</td>
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<td>LUNCH</td>
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<td>Time</td>
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<td>13:45–14:20</td>
<td>M7</td>
<td><strong>Stephan Appelt</strong> <em>(Forschungszentrum Jülich, DE)</em> From laser physics to the parahydrogen-pumped RASER</td>
<td></td>
</tr>
<tr>
<td>14:20–14:40</td>
<td>M8/P109</td>
<td><strong>Anu Kantola</strong> <em>(University of Oulu, FI)</em> Continuous-flow SABRE polarization for nuclear magnetic resonance and nuclear spin-induced magneto-optic experiments</td>
<td></td>
</tr>
<tr>
<td>14:40–15:00</td>
<td>M9/P32</td>
<td><strong>Karel Kouřil</strong> <em>(University of Southampton, UK)</em> Spin–isomer conversion in water–endofullerene at room temperature</td>
<td></td>
</tr>
<tr>
<td>15:00–15:20</td>
<td>M10/P34</td>
<td><strong>James MacDonald</strong> <em>(University of Nottingham, UK)</em> Hyperpolarisation using the Brute Force Approach</td>
<td></td>
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<tr>
<td>15:40–17:00</td>
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<td><strong>TEA and POSTERS</strong></td>
<td></td>
</tr>
<tr>
<td>17:00–17:45</td>
<td>M12</td>
<td><strong>Anne Lesage</strong> <em>(ENS Lyon, FR)</em> DNP–enhanced solid–state NMR spectroscopy at high magnetic field and fast MAS</td>
<td></td>
</tr>
<tr>
<td>17:45–18:05</td>
<td>M13/P126</td>
<td><strong>Jörg Heiliger</strong> <em>(Goethe University, Frankfurt, DE)</em> Site–directed spin labeling of partially and fully deuterated proteins with Gd(III) for site–selective MAS DNP</td>
<td></td>
</tr>
<tr>
<td>18:05–18:25</td>
<td>M14/P118</td>
<td><strong>Ying Chow</strong> <em>(FMP Berlin, DE)</em> DNP–enhanced solid–state NMR enables observation of collagen triple–helix structural change in human alkaptonuria cartilage</td>
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<td>19:30</td>
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<td><strong>DINNER</strong></td>
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<tr>
<td>9:00–9:45</td>
<td>T1</td>
<td>Sami Jannin (University of Lyon, FR)</td>
<td>Astonishing dissolution dynamic nuclear polarization</td>
</tr>
<tr>
<td>9:45–10:05</td>
<td>T2</td>
<td>Benno Meier (University of Southampton, UK)</td>
<td>Sub-second dissolution–DNP at minimal dilution</td>
</tr>
<tr>
<td>10:05–10:25</td>
<td>T3</td>
<td>Andrea Capozzi (DTU Copenhagen, DK)</td>
<td>A narrow line UV–induced non-persistent radical to generate highly polarized transportable glucose solid samples</td>
</tr>
<tr>
<td>10:25–11:00</td>
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<td>COFFEE</td>
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<tr>
<td>11:00–11:20</td>
<td>T4</td>
<td>Yifan Quan (PSI, CH)</td>
<td>Transportable hydrogen solid state nuclear polarization</td>
</tr>
<tr>
<td>11:20–11:40</td>
<td>T5</td>
<td>Nobuhiro Yanai (Kyushu University, JP)</td>
<td>Triplet DNP of nanoporous metal–organic frameworks</td>
</tr>
<tr>
<td>11:40–12:15</td>
<td>T6</td>
<td>Arnaud Comment (University of Cambridge, UK)</td>
<td>Developing novel methods for metabolic imaging by hyperpolarized $^{13}$C MR</td>
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<tr>
<td>12:15–13:45</td>
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<td>13:45–14:20</td>
<td>T7</td>
<td>Tom Wenckebach (PSI, CH)</td>
<td>Dynamic nuclear polarization beyond the high-temperature approximation</td>
</tr>
<tr>
<td>14:20–14:40</td>
<td>T8 P33</td>
<td>Christian Bengs (University of Southampton, UK)</td>
<td>Master equation for spin systems far from equilibrium</td>
</tr>
<tr>
<td>14:40–15:00</td>
<td>T9 P35</td>
<td>Federica Raimondi (University of Nottingham, UK)</td>
<td>Many-body kinetics of dynamic nuclear polarization by the cross effect</td>
</tr>
<tr>
<td>15:00–15:35</td>
<td>T10</td>
<td>Armin Purea (Bruker Biospin, DE)</td>
<td>Augmenting the mm wave field in MAS DNP</td>
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<tr>
<td>15:35–17:00</td>
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<td>TEA and POSTERS</td>
<td></td>
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<tr>
<td>17:00–17:45</td>
<td>T11</td>
<td>Leif Schröder (FMP Berlin, DE)</td>
<td>Host Structures and their detection schemes for molecular sensing with reversibly bound xenon</td>
</tr>
<tr>
<td>17:45–18:05</td>
<td>T12 P77</td>
<td>Claudia Zanella (EPFL, CH)</td>
<td>Boosting $^{129}$Xe DNP efficiency using ultrasonic sample mixing and microwave frequency modulation</td>
</tr>
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<td>19:30</td>
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<td>DINNER</td>
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<td>Time</td>
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<td>9:00–9:45</td>
<td>W1</td>
<td>Fedor Jelezko (University of Ulm, DE)</td>
<td>High sensitivity NMR enabled by diamond colour centers</td>
</tr>
<tr>
<td>9:45–10:05</td>
<td>W2/P62</td>
<td>Ashok Ajoy (University of California, Berkeley, US)</td>
<td>Optical $^{13}$C hyperpolarization in powdered diamond</td>
</tr>
<tr>
<td>10:05–10:25</td>
<td>W3/P72</td>
<td>Antoine Garcon (Helmholtz Institute, Mainz, DE)</td>
<td>Dark matter searches via ultralow-field nuclear magnetic resonance (CASPER)</td>
</tr>
<tr>
<td>10:25–11:00</td>
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<td>COFFEE</td>
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</tr>
<tr>
<td>11:00–11:20</td>
<td>W4/P68</td>
<td>Bo Zhang (University of Science and Technology of China, CN)</td>
<td>Mesoscopic magnetic resonance spectroscopy with a remote spin sensor</td>
</tr>
<tr>
<td>11:20–11:40</td>
<td>W5/P75</td>
<td>Peter Rakitzis (IELS–FORTH, Heraklion, GR)</td>
<td>High–density spin–polarized H and D from UV photodissociation, and spin–polarized molecules from IR rovibrational excitation</td>
</tr>
<tr>
<td>11:40–12:15</td>
<td>W6/P79</td>
<td>Peter Blümler (University of Mainz, DE)</td>
<td>Nuclear hyperpolarization of $^3$He in magnetized plasma</td>
</tr>
<tr>
<td>12:15–13:45</td>
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<td>LUNCH</td>
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<tr>
<td>Time</td>
<td>Session</td>
<td>Speaker</td>
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<tr>
<td>13:45–14:20</td>
<td>W7</td>
<td>Gaël de Paëpe (University of Grenoble, FR)</td>
<td>Hypersensitivity with DNP: natural isotopic abundance and closed-loop cryogenic He sample spinning</td>
</tr>
<tr>
<td>14:20–14:40</td>
<td>W8 P110</td>
<td>Snaedis Björgvinsdóttir (EPFL, CH)</td>
<td>Bulk nuclear hyperpolarization of inorganic solids</td>
</tr>
<tr>
<td>14:40–15:00</td>
<td>W9 P134</td>
<td>J. Ole Brauckmann (Radboud University, NL)</td>
<td>A low-temperature (25K) MAS DNP setup for materials studies</td>
</tr>
<tr>
<td>15:00–15:35</td>
<td>W10</td>
<td>Marek Pruski (Ames Laboratory, Iowa, US)</td>
<td>Advances in atomic-scale characterization of materials surfaces by DNP-enhanced solid–state NMR</td>
</tr>
<tr>
<td>15:35–17:00</td>
<td></td>
<td><strong>TEA and POSTERS</strong></td>
<td></td>
</tr>
<tr>
<td>17:00–17:20</td>
<td>W11 P43</td>
<td>Tomas Orlando (MPI Göttingen, DE)</td>
<td>Scalar $^{13}$C–Overhauser DNP in the liquid state at low and high magnetic fields</td>
</tr>
<tr>
<td>17:20–17:40</td>
<td>W12 P123</td>
<td>Alessandra Lucini Paioni (Utrecht University, NL)</td>
<td>Spatial localization and selectivity in dynamic nuclear polarization</td>
</tr>
<tr>
<td>19:30</td>
<td></td>
<td><strong>CONFERENCE DINNER</strong></td>
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</tbody>
</table>
ORAL PRESENTATIONS

Contributors may run their presentation on their own laptop or use a Mac or Windows laptop provided at the conference. In the latter case, the presentations must be loaded onto the conference laptops by no later than:

- 08:45 if your talk is during the morning session
- 13:30 if your talk is during an afternoon session

A speaker preview room is available on the first floor to upload and check your presentation. This room will be open only at the following times:

- Sunday from 10:00 to 16:00
- Monday to Wednesday from 8:00 to 8:45 and from 13:00 to 13:30

POSTERS

Poster Sessions run from Monday 3rd to Wednesday 5th during the tea break in the interval 15:40-17:00. Posters need to be on display by Monday 15:00 and must be removed by Wednesday 19:30 at the latest. Fixing materials will be provided.

FOOD AND DRINK

LUNCHES

Lunches from Monday to Wednesday are included in the registration fees. Lunch is served as a buffet in the hotel restaurant on the ground floor (indicated in the map provided in this booklet). Lunches run from 12:15 to 13:45 each day.

DRINKS

You will be provided with 4 drink tokens. You can exchange these for a drink (beer/wine/soft drink) at the hotel bars each day, in the interval 18:30-19:30 just before dinner.

DINNERS

A 3-course dinner per night (from Sunday to Wednesday) is included in the registration fees. Dinner is served in the conference hall from 19:30 every night. One drink (glass of wine/beer/soft drink) is included but you can purchase more if needed! For the Wed conference dinner you are entitled to half a bottle of wine per person. Remember to get up for your onward travel on Thursday!
AWARDS

We congratulate the following students on the following travel awards, allocated by the HYP18 Scientific Committee. We thank AMPERE and ISMAR for sponsoring these awards.

AMPERE STUDENT TRAVEL AWARDS

• Danhua Dai
• Théo El Darai
• Arianna Ferrari
• Anne Friebel
• Krishnendu Kundu
• Claudia Zanella

ISMAR STUDENT TRAVEL AWARDS

• Patrick Kurle
• Otto Mankinen
• Lutoslawa Mikowska
• Oleg Salnikov

JMR-ISMAR YOUNG SCIENTIST AWARD

The Journal of Magnetic Resonance and the International Society of Magnetic Resonance (ISMAR) sponsor a series of awards for outstanding young scientists active in the field of magnetic resonance. Each award consists of: a US$500 check, a one year electronic subscription to the Journal of Magnetic Resonance, and a Certificate. The awardees are invited and encouraged by JMR and ISMAR to submit their work to JMR (any article type). These submissions will undergo the regular editorial process including peer review.

One JMR-ISMAR award will be made during HYP18. The recipient will be announced during the conference.
<table>
<thead>
<tr>
<th>number</th>
<th>presenter</th>
<th>title</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Felix Kreis</td>
<td>B1-insensitive partial hyperpolarization transfer in [2-13C]pyruvate</td>
</tr>
<tr>
<td>P2</td>
<td>Justin Lau</td>
<td>A 3D Hybrid-shot spiral for hyperpolarized 13C imaging (3D-HYSS)</td>
</tr>
<tr>
<td>P3</td>
<td>Leslie Mazuel</td>
<td>[1-13C]glutamate hyperpolarisation for metabolism study in the rodent brain using magnetic resonance spectroscopy (MRS)</td>
</tr>
<tr>
<td>P4</td>
<td>Jack Miller</td>
<td>In vivo characterisation and synthesis of hyperpolarized [2,2-2H2,1,3-13C2]acetoacetate</td>
</tr>
<tr>
<td>P5</td>
<td>Mor Mishkovsky</td>
<td>Direct detection of glucose metabolism in vivo in human GBM mice models by hyperpolarized [3H7, 13C6]glucose</td>
</tr>
<tr>
<td>P6</td>
<td>Thanh Phong Lê</td>
<td>Probing real-time metabolism and neuroprotection of hyperpolarized L-[1-13C]-lactate in a mouse model of stroke</td>
</tr>
<tr>
<td>P7</td>
<td>Alice Radaelli</td>
<td>Probing renal pH using hyperpolarized [1-13C]alaminamide</td>
</tr>
<tr>
<td>P8</td>
<td>Yoichi Takakusagi</td>
<td>Hyperpolarized [1-13C]pyruvate MRS reveals increased aerobic glycolysis in the ultra-early phase of PSA-negative prostate carcinogenesis</td>
</tr>
<tr>
<td>P9</td>
<td>Hikari Yoshihara</td>
<td>Renal metabolism of hyperpolarized [1-13C]aspartate</td>
</tr>
<tr>
<td>P10</td>
<td>Emmanuelle Flatt</td>
<td>Exploring the potential of hyperpolarized 6Li to study lithium bio-distribution in the rat brain</td>
</tr>
<tr>
<td>P11</td>
<td>Anne Frahm</td>
<td>Analysis of dDNP NMR metabolic data from cancer cells</td>
</tr>
<tr>
<td>P13</td>
<td>Jeremy Gordon</td>
<td>Hyperpolarized 13C MRI of the human brain</td>
</tr>
<tr>
<td>P14</td>
<td>Magnus Karlsson</td>
<td>Hyperpolarized 133Cs ions for investigating membrane impairment in cells</td>
</tr>
<tr>
<td>P15</td>
<td>Olivier Cala</td>
<td>Interaction studies with secondary-labelled hyperpolarized ligands</td>
</tr>
<tr>
<td>P16</td>
<td>Martin Grashei</td>
<td>pH-Dependancy of the spin-lattice relaxation constant (T1) of 13C-labelled hyperpolarized biomolecules</td>
</tr>
<tr>
<td>P17</td>
<td>Filippo Caracciolo</td>
<td>Dynamic nuclear polarization of 13C and 3H β-cyclodextrins</td>
</tr>
<tr>
<td>P18</td>
<td>Théo El Darai</td>
<td>Generating persistent hyperpolarization with porous polarizing polymers</td>
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<tr>
<td>P19</td>
<td>Arianna Ferrari</td>
<td>Counterintuitive design of non-structured-Hybrid Polarizing Solids for dynamic nuclear polarization</td>
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<tr>
<td>P20</td>
<td>Sami Jannin</td>
<td>Microwave-gated dissolution dynamic nuclear polarization</td>
</tr>
<tr>
<td>P21</td>
<td>Lionel Arn</td>
<td>Boosting the dynamical nuclear polarization of [1-13C]butyrate with microwave frequency modulation</td>
</tr>
<tr>
<td>P22</td>
<td>Pernille Rose Jensen</td>
<td>Stable isotope-resolved analysis with quantitative dDNP</td>
</tr>
<tr>
<td>P23</td>
<td>Mohammed Albannay</td>
<td>Low microwave attenuation and low thermal loss waveguides for dDNP probes</td>
</tr>
<tr>
<td>P24</td>
<td>Mohammed Albannay</td>
<td>Versatile polarizer NMR spectrometer</td>
</tr>
<tr>
<td>P25</td>
<td>Morgan Ceillier</td>
<td>High-performance fluid-path for dissolution-DNP</td>
</tr>
<tr>
<td>P26</td>
<td>Tian Cheng</td>
<td>Refrigerated-bath cryostat for dissolution dynamic nuclear polarization</td>
</tr>
<tr>
<td>P27</td>
<td>Behdad Aghelnejad</td>
<td>Hyperfine EPR spectroscopy of nitroxides in DNP-water-glycerol mixtures reveals clustering of radicals</td>
</tr>
<tr>
<td>P28</td>
<td>Behdad Aghelnejad</td>
<td>Transferring frozen hyperpolarized droplets for dissolution DNP</td>
</tr>
<tr>
<td>P29</td>
<td>Benno Meier</td>
<td>Sub-second dissolution-DNP at minimal dilution</td>
</tr>
<tr>
<td>P30</td>
<td>James Eills</td>
<td>Application of bullet-DNP to produce long-lived hyperpolarized fumarate</td>
</tr>
<tr>
<td>P31</td>
<td>George Bacanu</td>
<td>Towards quantum-rotor-induced polarization in CH4@C60, methane-endofullerene complex</td>
</tr>
<tr>
<td>P32</td>
<td>Karel Kouřil</td>
<td>Spin-isomer conversion in water-endofullerene at room temperature</td>
</tr>
<tr>
<td>P33</td>
<td>Christian Bengs</td>
<td>Master-equation for spin systems far from equilibrium</td>
</tr>
<tr>
<td>P34</td>
<td>James MacDonald</td>
<td>Hyperpolarisation using the brute force approach</td>
</tr>
<tr>
<td>P35</td>
<td>Federica Raimondi</td>
<td>Many-body kinetics of dynamic nuclear polarization by the cross effect</td>
</tr>
<tr>
<td>P36</td>
<td>Krishnendu Kundu</td>
<td>Electron spectral diffusion and DNP – simulations and experiments</td>
</tr>
<tr>
<td>P37</td>
<td>Takayuki Kumada</td>
<td>Proton hyperpolarization for polarized neutron scattering</td>
</tr>
<tr>
<td>P38</td>
<td>Danhua Dai</td>
<td>Experimental access to the microwave saturation factor at 9.4 Tesla DNP in liquid state</td>
</tr>
<tr>
<td>P39</td>
<td>Vasyl Denysenko</td>
<td>Compact DNP polarizer for MRI Applications at 1.5 T</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>P40</td>
<td>Thierry Dubroca</td>
<td>High enhancement and large volume overhauser liquid DNP at 14.1 T</td>
</tr>
<tr>
<td>P41</td>
<td>Raphael Kircher</td>
<td>Dynamic nuclear polarization enables NMR reaction/process monitoring in the fast flow regime</td>
</tr>
<tr>
<td>P42</td>
<td>Raphael Kircher</td>
<td>Fighting the lifetime issue of NMR hyperpolarisation</td>
</tr>
<tr>
<td>P43 W11</td>
<td>Tomas Orlando</td>
<td>Scalar $^{13}$C-Overhauser DNP in the liquid state at low and high magnetic fields</td>
</tr>
<tr>
<td>P44</td>
<td>Lynda Brown</td>
<td>Synthesis of molecules in pursuit of long lived nuclear singlet states</td>
</tr>
<tr>
<td>P45</td>
<td>Stuart Elliott</td>
<td>Field-cycling long-lived-state NMR of $^{15}$N$_2$ spin pairs</td>
</tr>
<tr>
<td>P46</td>
<td>Mohamed Sabba</td>
<td>Ab Initio computational modelling of singlet relaxation times using Gaussian and Mathematica</td>
</tr>
<tr>
<td>P47</td>
<td>Shinsuke Sando</td>
<td>Design of long-lived hyperpolarized molecular probes and applications</td>
</tr>
<tr>
<td>P48</td>
<td>Manvendra Sharma</td>
<td>High-performance modular probe assemblies for microfluidic nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>P49</td>
<td>Frederike Euchner</td>
<td>Comparison of the hyperpolarization of different fluorinated aromatic systems via photo-CIDNP</td>
</tr>
<tr>
<td>P50</td>
<td>Lars Kuhn</td>
<td>Hyperpolarization-enhanced 2D NMR observation of protein folding in real time</td>
</tr>
<tr>
<td>P51</td>
<td>Patrick Kurle</td>
<td>Photo-CIDNP and recovery studies on tryptophan-labelled aureochrome LOV</td>
</tr>
<tr>
<td>P52</td>
<td>Christopher Wedge</td>
<td>Exploiting radical triplet pair hyperpolarization for sensitivity enhancement in solution state NMR</td>
</tr>
<tr>
<td>P53 M3</td>
<td>Alexandra Yurkovskaya</td>
<td>Light-Induced hyperpolarization in reversible reactions of biomolecules</td>
</tr>
<tr>
<td>P54</td>
<td>Saket Patel</td>
<td>Development of UV-induced non-persistent radicals for dissolution dynamic nuclear polarization</td>
</tr>
<tr>
<td>P55 T3</td>
<td>Andrea Capozzi</td>
<td>A narrow line UV-induced non-persistent radical to generate highly polarized transportable glucose solid samples</td>
</tr>
<tr>
<td>P56</td>
<td>Saiya Fujiwara</td>
<td>DNP of metal-organic frameworks using photo-excited triplet electrons</td>
</tr>
<tr>
<td>P57</td>
<td>Adam Gaunt</td>
<td>Photo-generated radicals on nitroso derivatives for dissolution DNP</td>
</tr>
<tr>
<td>P58</td>
<td>Irene Marco-Rius</td>
<td>Non-persistent, photo-generated radicals for high-yield DNP</td>
</tr>
<tr>
<td>P59</td>
<td>Akinori Kagawa</td>
<td>Room temperature hyperpolarization of equal mixtures of benzoic acid and other aromatic carboxylic acid</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P60</td>
<td>Yifan Quan</td>
<td>Transportable hydrogen solid state nuclear polarization</td>
</tr>
<tr>
<td>P61</td>
<td>Kenichiro Tateishi</td>
<td>DNP with photo-excited triplet electron using soluble pentacene derivatives</td>
</tr>
<tr>
<td>P62</td>
<td>Ashok Ajoy</td>
<td>Optical $^{13}$C hyperpolarization In powdered diamond</td>
</tr>
<tr>
<td>P63</td>
<td>Koichiro Miyanishi</td>
<td>Long-lived state of four-spin system hyperpolarized at room temperature</td>
</tr>
<tr>
<td>P64</td>
<td>Maosen Guo</td>
<td>Nanoscale magnetic resonance imaging of intracellular proteins</td>
</tr>
<tr>
<td>P65</td>
<td>Rui Li</td>
<td>Wide-band microwave magnetometry using a nitrogen vacancy center in diamond</td>
</tr>
<tr>
<td>P66</td>
<td>Murari Soundararajan</td>
<td>100-Fold $^{13}$C DNP Enhancement in diamond nanopowder at 9 T</td>
</tr>
<tr>
<td>P67</td>
<td>Grzegorz Kwiatkowski</td>
<td>Exploiting endogenous paramagnetic surface defects for the direct dynamic nuclear polarization of micro/nanocrystals of silicon and diamonds</td>
</tr>
<tr>
<td>P68</td>
<td>Bo Zhang</td>
<td>Mesoscopic magnetic resonance spectroscopy with a remote spin sensor</td>
</tr>
<tr>
<td>P69</td>
<td>Jeong Hyun Shim</td>
<td>Hyperpolarization of nanodiamonds at 0.32 T and 3.3 K</td>
</tr>
<tr>
<td>P70</td>
<td>Jeong Hyun Shim</td>
<td>Overhauser dynamic nuclear polarization at nearly zero magnetic field</td>
</tr>
<tr>
<td>P71</td>
<td>Fazhan Shi</td>
<td>Electron spin resonance spectroscopy of a single molecule</td>
</tr>
<tr>
<td>P72</td>
<td>Antoine Garcon</td>
<td>Dark matter searches via ultralow-field nuclear magnetic resonance (CASPER)</td>
</tr>
<tr>
<td>P73</td>
<td>Takeshi Inoue</td>
<td>Development of an optical magnetometer toward highly sensitive magnetometry</td>
</tr>
<tr>
<td>P74</td>
<td>G Rajalakshmi</td>
<td>Development of a Rb optical magnetometer for low-field NMR studies</td>
</tr>
<tr>
<td>P75</td>
<td>Peter Rakitzis</td>
<td>High-density spin-polarized H and D from UV photodissociation, and spin-polarized molecules from IR rovibrational excitation</td>
</tr>
<tr>
<td>P76</td>
<td>Jean-Noel Hyacinthe</td>
<td>LOD-ESR investigation of trityl-doped $^{129}$Xe DNP samples at 6.7 T and 1.1 K</td>
</tr>
<tr>
<td>P77</td>
<td>Claudia Zanella</td>
<td>Boosting $^{129}$Xe DNP efficiency using ultrasonic sample mixing and microwave frequency modulation</td>
</tr>
<tr>
<td>P78</td>
<td>Jonathan Birchall</td>
<td>Understanding Rb And Cs spin-exchange optical pumping for application to hyperpolarised $^{129}$Xe functional lung imaging</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P79 W6</td>
<td>Peter Blümler</td>
<td>Method for fast, efficient and continuous application of hyperpolarized $^{129}$Xe in aqueous and biocompatible liquids</td>
</tr>
<tr>
<td>P80</td>
<td>Thomas Meersmann</td>
<td>Hp $^{129}$Xe relaxation, flow, and dispersion studies in catalytic reactors</td>
</tr>
<tr>
<td>P81</td>
<td>Lutosława Mikowska</td>
<td>$^3$He and $^{129}$Xe polarizers for medical applications</td>
</tr>
<tr>
<td>P82 S3</td>
<td>Eleonora Cavallari</td>
<td>First in cellulo and in vivo metabolic studies using parahydrogen hyperpolarized [1-$^{13}$C]pyruvate</td>
</tr>
<tr>
<td>P83 M4</td>
<td>Danila Barskiy</td>
<td>Metal-free parahydrogen-based hyperpolarized contrast agents produced via rapid catalyst capture</td>
</tr>
<tr>
<td>P84</td>
<td>Bernhard Bluemich</td>
<td>Continuous hyperpolarization with parahydrogen in a membrane reactor</td>
</tr>
<tr>
<td>P85 M5</td>
<td>James Eills</td>
<td>Field-swept polarization transfer in parahydrogen NMR</td>
</tr>
<tr>
<td>P86</td>
<td>Anne Friebel</td>
<td>Signal-enhanced medium-field NMR Spectroscopy By parahydrogen induced polarization (PHIP)</td>
</tr>
<tr>
<td>P87</td>
<td>Dariusz Golowicz</td>
<td>Time-resolved NUS interleaved acquisition on benchtop spectrometer under PHIP condition in a continuous-flow system</td>
</tr>
<tr>
<td>P88</td>
<td>Boyd Goodson</td>
<td>From cleavable “double agents” to polarized targets: New systems and approaches for SABRE and SEOP hyperpolarization</td>
</tr>
<tr>
<td>P89</td>
<td>William Hale</td>
<td>PHIP on a CHIP – hyperpolarisation in microfluidic NMR</td>
</tr>
<tr>
<td>P90</td>
<td>Julia Hollenbach</td>
<td>Carbenes - a novel group of molecules for the metal free activation of parahydrogen?</td>
</tr>
<tr>
<td>P91</td>
<td>Julia Hollenbach</td>
<td>Hyperpolarisation on Tap – towards the construction of a continuous-flow polariser for the production of hyperpolarised metabolites</td>
</tr>
<tr>
<td>P92</td>
<td>Gaspard Huber</td>
<td>Ultrafast 2D NMR analysis of SABRE-hyperpolarised mixtures</td>
</tr>
<tr>
<td>P93</td>
<td>Konstantin Ivanov</td>
<td>Anti-phase spin order of H$_2$ in high-field experiments with parahydrogen and its manifestations in SABRE-derived polarization</td>
</tr>
<tr>
<td>P94</td>
<td>Sergey Korchak</td>
<td>Over 60% $^{13}$C polarization by pulsed parahydrogen-induced polarization and sidearm hydrogenation</td>
</tr>
<tr>
<td>P95</td>
<td>Hana Kouřilová</td>
<td>Towards PHIP-hyperpolarized 1-$^{13}$C-pyruvate</td>
</tr>
<tr>
<td>P96</td>
<td>Salvatore Mamone</td>
<td>A pulsed PHIP approach for hyperpolarizing metabolites</td>
</tr>
<tr>
<td>P97</td>
<td>Otto Mankinen</td>
<td>Hyperpolarized ultrafast Laplace NMR</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P98</td>
<td>Andrey Pravdivtsev</td>
<td>Refocused And Double Refocused Only Parahydrogen Spectroscopy (ROPSYz AND DROPSYd)</td>
</tr>
<tr>
<td>P99</td>
<td>Oleg Salnikov</td>
<td>$^{13}$C parahydrogen-induced polarization of acetates and pyruvates</td>
</tr>
<tr>
<td>P100</td>
<td>Stephan Knecht</td>
<td>Kinetics of spin order in SABRE systems at high-fields</td>
</tr>
<tr>
<td>P101</td>
<td>Jennifer Lewis</td>
<td>$^{19}$F hyperpolarisation by Signal Amplification By Reversible Exchange</td>
</tr>
<tr>
<td>P102</td>
<td>Adam Mames</td>
<td>Capabilities and limitations of oligopeptides NMR Signal Amplification By Reversible Exchange</td>
</tr>
<tr>
<td>P103</td>
<td>Ryan Mewis</td>
<td>Forensic hyperpolarization: detecting fentanyl and its pyridyl analogues</td>
</tr>
<tr>
<td>P104</td>
<td>Markus Plaumann</td>
<td>SABRE-based hyperpolarization and substituent effects</td>
</tr>
<tr>
<td>P105</td>
<td>Thomas Robertson</td>
<td>Heterogeneous SABRE catalyst deactivation with resultant T$_1$ lengthening of the analyte</td>
</tr>
<tr>
<td>P106</td>
<td>Emma Stanbury</td>
<td>Quantifying the effect of substrate-iridium binding potential via pK$_a$ on SABRE hyperpolarisation</td>
</tr>
<tr>
<td>P107</td>
<td>Marco Tessari</td>
<td>Quantitative NMR analysis at nanomolar concentrations via Para-Hydrogen Induced Hyperpolarization</td>
</tr>
<tr>
<td>P108</td>
<td>Ewoud Vaneechtaute</td>
<td>Cyclic coherent hyperpolarisation of water with pH$_2$</td>
</tr>
<tr>
<td>P109 M8</td>
<td>Anu Kantola</td>
<td>Continuous-flow SABRE polarization for nuclear magnetic resonance and nuclear spin-induced magneto-optic experiments</td>
</tr>
<tr>
<td>P110 W8</td>
<td>Snaedis Björgvinsdòttir</td>
<td>Bulk nuclear hyperpolarization of inorganic solids</td>
</tr>
<tr>
<td>P111</td>
<td>Frédéric Blanc</td>
<td>Solids DNP of insensitive nuclei and challenging materials</td>
</tr>
<tr>
<td>P112</td>
<td>Olivier Lafon</td>
<td>DNP-NMR of dissolved organic matter and bio-inspired heterogeneous catalysts</td>
</tr>
<tr>
<td>P113</td>
<td>Subhradip Paul</td>
<td>Dynamic nuclear polarisation enhanced solid-state NMR studies of catalytic materials and small organic molecules</td>
</tr>
<tr>
<td>P114</td>
<td>Arthur Pinon</td>
<td>Structure of core-shell nanoparticles determined by relayed DNP NMR</td>
</tr>
<tr>
<td>P115</td>
<td>Philipp Schleker</td>
<td>Surface structural study of N-doped hydrothermal carbon (N-HTC) by isotopic enrichment and DNP-SENS (Dynamic Nuclear Polarization Surface-Enhanced NMR Spectroscopy)</td>
</tr>
<tr>
<td>P116</td>
<td>Daphna Shimon</td>
<td>Dynamic nuclear polarization of Si microparticles using structural defects</td>
</tr>
<tr>
<td>P117</td>
<td>Pierre Thureau</td>
<td>Investigating small particles of organic powders using MAS dynamic nuclear polarization</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P118 M14</td>
<td>Wing Ying Chow</td>
<td>DNP-Enhanced solid-state NMR enables observation of collagen triple helix structural change in human Alkaptonuria cartilage</td>
</tr>
<tr>
<td>P119</td>
<td>Galia Debelouchina</td>
<td>DNP polarization agents for the cellular milieu: new chemistries and approaches</td>
</tr>
<tr>
<td>P120</td>
<td>Thomas Deo</td>
<td>Structural studies of amyloid-beta interacting with cell membrane using magic-angle spinning DNP</td>
</tr>
<tr>
<td>P121</td>
<td>Henrike Heise</td>
<td>Conformational ensembles of disordered proteins: A glimpse into chaos at high sensitivity</td>
</tr>
<tr>
<td>P122</td>
<td>Vojč Kocman</td>
<td>High-resolution structures of multiple folds adopted by GGGAGCG repeat rich oligonucleotides</td>
</tr>
<tr>
<td>P123 W12</td>
<td>Alessandra Lucini Paioni</td>
<td>Spatial localization and selectivity in dynamic nuclear polarization</td>
</tr>
<tr>
<td>P124</td>
<td>Philip Williamson</td>
<td>Proton detected magic-angle spinning dynamic nuclear polarization NMR for the analysis of natural abundance biopolymers</td>
</tr>
<tr>
<td>P125</td>
<td>Claudia Avalos</td>
<td>$^{19}$F Solid-state dynamic nuclear polarization enhanced NMR</td>
</tr>
<tr>
<td>P126 M13</td>
<td>Jörg Heiliger</td>
<td>Site-directed spin labeling of partially and fully deuterated proteins with Gd(III) for site-selective MAS DNP</td>
</tr>
<tr>
<td>P127</td>
<td>Moreno Lelli</td>
<td>Efficient solid-state DNP at high field, fast MAS and high temperature: narrow-line radicals and the role of spin diffusion</td>
</tr>
<tr>
<td>P128</td>
<td>Alicia Lund</td>
<td>Tuning electronic spin properties of BDPA-nitroxide biradicals for efficient cross effect DNP at magnetic fields up to 21.1 T</td>
</tr>
<tr>
<td>P129</td>
<td>Sucharita Mandal</td>
<td>Synthesis of BDPA radicals and investigation of their stability</td>
</tr>
<tr>
<td>P130</td>
<td>Guinevere Mathies</td>
<td>The conformation of bis-nitroxide polarizing agents by multi-frequency EPR spectroscopy</td>
</tr>
<tr>
<td>P131</td>
<td>Olivier Ouari</td>
<td>DNP-enhanced SSNMR sensitivity: Improved polarizing agents for high fields</td>
</tr>
<tr>
<td>P132</td>
<td>Svetlana Pylaeva</td>
<td>Electronic structure of BDPA radical in connection to OE-DNP</td>
</tr>
<tr>
<td>P133</td>
<td>Gabriele Stevanato</td>
<td>An efficient Gd$^{3+}$ based complex for high field Dynamic Nuclear Polarization</td>
</tr>
<tr>
<td>P134 W9</td>
<td>Ole Brauckmann</td>
<td>A low temperature (25K) MAS DNP setup for materials studies</td>
</tr>
<tr>
<td>P135</td>
<td>Ivan Sergeyev</td>
<td>263 GHz klystron: A lower-cost route to dynamic nuclear polarization</td>
</tr>
<tr>
<td>P136</td>
<td>Thorsten Maly</td>
<td>DNP NMR spectroscopy using a 263 GHz integrated THz system</td>
</tr>
</tbody>
</table>
 PARTICIPANTS  

*In the case of posters, only the presenter is listed*

ASTA = Ampère Student Travel Award  
ISTA = ISMAR Student Travel Award

<table>
<thead>
<tr>
<th>name</th>
<th>affiliation</th>
<th>country</th>
<th>activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behdad Aghelnejad</td>
<td>Bruker Biospin/ École normale supérieure</td>
<td>FR</td>
<td>P27, P28</td>
</tr>
<tr>
<td>Ashok Ajoy</td>
<td>UC Berkeley</td>
<td>US</td>
<td>W2, P62</td>
</tr>
<tr>
<td>Mohammed Albannay</td>
<td>Technical University of Denmark</td>
<td>DK</td>
<td>P23, P24</td>
</tr>
<tr>
<td>Stephan Appelt</td>
<td>Forschungszentrum Jülich</td>
<td>DE</td>
<td>M7</td>
</tr>
<tr>
<td>Jan Henrik Ardenkjær-Larsen</td>
<td>Technical University of Denmark</td>
<td>DK</td>
<td>SciComm, Chair (Tues AM)</td>
</tr>
<tr>
<td>Lionel Arn</td>
<td>University of Lausanne</td>
<td>CH</td>
<td>P21</td>
</tr>
<tr>
<td>Fabien Aussenac</td>
<td>BRUKER</td>
<td>FR</td>
<td></td>
</tr>
<tr>
<td>Claudia Avalos</td>
<td>École Polytechnique Fédérale de Lausanne (EPFL)</td>
<td>CH</td>
<td>P123</td>
</tr>
<tr>
<td>George Bacanu</td>
<td>University of Southampton</td>
<td>UK</td>
<td>P31</td>
</tr>
<tr>
<td>Marc Baldus</td>
<td>University of Utrecht</td>
<td>NL</td>
<td>SciComm, Chair (Wed PM)</td>
</tr>
<tr>
<td>Danila Barskiy</td>
<td>UC Berkeley</td>
<td>US</td>
<td>M4, P83</td>
</tr>
<tr>
<td>Christian Bengs</td>
<td>University of Southampton</td>
<td>UK</td>
<td>T8, P33</td>
</tr>
<tr>
<td>Jonathan Birchall</td>
<td>University of Nottingham</td>
<td>UK</td>
<td>P78</td>
</tr>
<tr>
<td>Snaedis Björgvinsdöttir</td>
<td>École Polytechnique Fédérale de Lausanne (EPFL)</td>
<td>CH</td>
<td>W8, P110</td>
</tr>
<tr>
<td>Frédéric Blanc</td>
<td>University of Liverpool</td>
<td>UK</td>
<td>P111</td>
</tr>
<tr>
<td>John Blanchard</td>
<td>Helmholtz-Institut Mainz</td>
<td>DE</td>
<td>SciComm, Chair (Wed AM)</td>
</tr>
<tr>
<td>Bernhard Bluemich</td>
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<td>IN</td>
<td>P74</td>
</tr>
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<td>Peter Rakitzis</td>
<td>IESL-FORTH</td>
<td>GR</td>
<td>W5, P75</td>
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<td>Mohamed Sabha</td>
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<td>UK</td>
<td>P46</td>
</tr>
<tr>
<td>Oleg Salnikov</td>
<td>International Tomography Center, SB RAS</td>
<td>RU</td>
<td>ISTA, P99</td>
</tr>
<tr>
<td>Shinsuke Sando</td>
<td>The University of Tokyo</td>
<td>JP</td>
<td>P47</td>
</tr>
<tr>
<td>Philipp Schleker</td>
<td>Max Planck Institute for Chemical Energy Conversion</td>
<td>DE</td>
<td>P115</td>
</tr>
<tr>
<td>Leif Schroeder</td>
<td>Leibniz-Forschungsinstitut fuer Molekulare Pharmakologie (FMP)</td>
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<td>T11</td>
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<td>Ivan Sergeyev</td>
<td>Bruker Biospin</td>
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<td>P135</td>
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<td>Manvendra Sharma</td>
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<td>UK</td>
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</tr>
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<td>Fazhan Shi</td>
<td>University of Science and Technology of China</td>
<td>CN</td>
<td>P71</td>
</tr>
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<td>Jeong Hyun Shim</td>
<td>Korea Research Institute of Standards and Science</td>
<td>KR</td>
<td>P69, P70</td>
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<td>country</td>
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<td>Daphna Shimon</td>
<td>Dartmouth College</td>
<td>US</td>
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</tr>
<tr>
<td>Murari Soundararajan</td>
<td>Ecole Polytechnique Fédérale de Lausanne (EPFL)</td>
<td>CH</td>
<td>P66</td>
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<td>Emma Stanbury</td>
<td>Centre for Hyperpolarisation in Magnetic Resonance, University of York</td>
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<td>Gabriele Stevanato</td>
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<td>P133</td>
</tr>
<tr>
<td>Yoichi Takakusagi</td>
<td>National Institute of Radiological Sciences (NIRS), National Institutes for Quantum and Radiological Science and Technology (QST)</td>
<td>JP</td>
<td>P8</td>
</tr>
<tr>
<td>Kenichiro Tateishi</td>
<td>RIKEN</td>
<td>JP</td>
<td>P61</td>
</tr>
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<td>Michael Taylor</td>
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<tr>
<td>Marco Tessari</td>
<td>Radboud University</td>
<td>NL</td>
<td>P107</td>
</tr>
<tr>
<td>Thomas Theis</td>
<td>North Carolina State University</td>
<td>US</td>
<td>M1</td>
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<tr>
<td>Pierre Thureau</td>
<td>Aix-Marseille Universite</td>
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<td>University of Huddersfield</td>
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<td>Tom Wenckebach</td>
<td>Paul Scherrer Institue</td>
<td>CH</td>
<td>T7</td>
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<td>Nobuhiro Yanai</td>
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<td>Hikari Yoshihara</td>
<td>Laboratory for Functional and Metabolic Imaging, Swiss Federal Institute of Technology, Lausanne</td>
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<td>Alexandra Yurkovskaya</td>
<td>International Tomography Center, Siberian Branch of Russian Academy of Sciences</td>
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<td>M3, P53</td>
</tr>
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<td>Claudia Zanella</td>
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<td>CH</td>
<td>ASTA, T12, P77</td>
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<td>W4, P68</td>
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</tbody>
</table>
HYP18
HYPERPOLARIZED MAGNETIC RESONANCE

2-5 September 2018
Grand Harbour Hotel
Southampton, UK
hyp18.com

CONFERENCE PROGRAM AND ABSTRACTS
# Detailed Program

A pdf of all talk and poster abstracts is available at hyp18.com

Codes Sn, Mn, Tn, Wn below refer to Sunday, Monday, Tuesday, Wednesday talks. Pn denotes a cross-reference to a poster.

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker/Institution</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:00-16:00</td>
<td>REGISTRATION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16:00-16:25</td>
<td></td>
<td>Opening Remarks: Malcolm Levitt</td>
<td></td>
</tr>
<tr>
<td>16:25-17:10</td>
<td>S1</td>
<td>John Kurhanewicz (University of San Francisco, US)</td>
<td>Hyperpolarized $^{13}$C MRI: Initial clinical applications</td>
</tr>
<tr>
<td>17:10-17:30</td>
<td>S2</td>
<td>Mor Mishkovsky (EPFL, CH)</td>
<td>Direct detection of glucose metabolism in vivo in human GBM mice models by hyperpolarized $^{2H_7,^{13}C_6}$-glucose</td>
</tr>
<tr>
<td>17:30-17:50</td>
<td>S3</td>
<td>Eleonora Cavallari (University of Turin, IT)</td>
<td>First in cellulo and in vivo metabolic studies using parahydrogen–hyperpolarized $[1-{^{13}C}]$-pyruvate</td>
</tr>
<tr>
<td>17:50-18:25</td>
<td>S4</td>
<td>Mathilde Lerche (DTU, Copenhagen, DK)</td>
<td>Metabolic signatures of living cells</td>
</tr>
<tr>
<td>19:30-21:00</td>
<td></td>
<td>DINNERS</td>
<td></td>
</tr>
<tr>
<td>21:00-21:35</td>
<td>S5</td>
<td>Kevin Brindle (University of Cambridge, UK)</td>
<td>Metabolic imaging with hyperpolarized $^{13}$C–labelled cell substrates – from mouse to man</td>
</tr>
<tr>
<td>Time</td>
<td>Session</td>
<td>Speaker/Institution</td>
<td>Topic</td>
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<tr>
<td>9:00-9:45</td>
<td>M1</td>
<td>Thomas Theis (Duke University, US)</td>
<td>SABRE of X-nuclei: from basic spin physics to future biosensing applications</td>
</tr>
<tr>
<td>9:45-10:05</td>
<td>M2</td>
<td>Stefan Glöggler (MPI Göttingen, US)</td>
<td>Parahydrogen Induced Polarization: over 50% $^1$H and $^{13}$C polarization of metabolite precursors and 12% $^{15}$N polarization with 20 minutes $T_1$ in water</td>
</tr>
<tr>
<td>10:05-10:25</td>
<td>M3/P53</td>
<td>Alexandra Yurkovskaya (ITC Novosibirsk, RU)</td>
<td>Light-induced hyperpolarization in reversible reactions of biomolecules</td>
</tr>
<tr>
<td>10:25-11:00</td>
<td></td>
<td>COFFEE</td>
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<tr>
<td>11:00-11:20</td>
<td>M4/P83</td>
<td>Danila Barskiy (UC Berkeley, US)</td>
<td>Metal-Free parahydrogen-based hyperpolarized contrast agents produced via rapid catalyst capture</td>
</tr>
<tr>
<td>11:20-11:40</td>
<td>M5/P85</td>
<td>James Eills (University of Southampton, UK)</td>
<td>Field-swept polarization transfer in parahydrogen NMR</td>
</tr>
<tr>
<td>11:40-12:15</td>
<td>M6</td>
<td>Meghan Halse (University of York, UK)</td>
<td>$^1$H and $^{13}$C benchtop NMR spectroscopy with SABRE hyperpolarisation</td>
</tr>
<tr>
<td>12:15-13:45</td>
<td></td>
<td>LUNCH</td>
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<td>Time</td>
<td>Session</td>
<td>Speaker</td>
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<td>13:45-14:20</td>
<td>M7</td>
<td>Stephan Appelt (Forschungszentrum Jülich, DE)</td>
<td>From laser physics to the parahydrogen-pumped RASER</td>
</tr>
<tr>
<td>14:20-14:40</td>
<td>M8</td>
<td>Anu Kantola (University of Oulu, FI)</td>
<td>Continuous-flow SABRE polarization for nuclear magnetic resonance and nuclear spin-induced magneto-optic experiments</td>
</tr>
<tr>
<td>14:40-15:00</td>
<td>M9</td>
<td>Karel Kouřil (University of Southampton, UK)</td>
<td>Spin–isomer conversion in water–endofullerene at room temperature</td>
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<tr>
<td>15:00-15:20</td>
<td>M10</td>
<td>James MacDonald (University of Nottingham, UK)</td>
<td>Hyperpolarisation using the Brute Force Approach</td>
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<tr>
<td>15:40-17:00</td>
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<td>TEA and POSTERS</td>
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<tr>
<td>17:00-17:45</td>
<td>M12</td>
<td>Anne Lesage (ENS Lyon, FR)</td>
<td>DNP–enhanced solid–state NMR spectroscopy at high magnetic field and fast MAS</td>
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<tr>
<td>17:45-18:05</td>
<td>M13</td>
<td>Jörg Heiliger (Goethe University, Frankfurt, DE)</td>
<td>Site–directed spin labeling of partially and fully deuterated proteins with Gd(III) for site–selective MAS DNP</td>
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<tr>
<td>18:05-18:25</td>
<td>M14</td>
<td>Ying Chow (FMP Berlin, DE)</td>
<td>DNP–enhanced solid–state NMR enables observation of collagen triple–helix structural change in human alkaptonuria cartilage</td>
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<td>9:00-9:45</td>
<td>T1</td>
<td>Sami Jannin (University of Lyon, FR)</td>
<td>Astonishing dissolution dynamic nuclear polarization</td>
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<tr>
<td>9:45-10:05</td>
<td>T2</td>
<td>Benno Meier (University of Southampton, UK)</td>
<td>Sub-second dissolution–DNP at minimal dilution</td>
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<tr>
<td>10:05-10:25</td>
<td>T3</td>
<td>Andrea Capozzi (DTU Copenhagen, DK)</td>
<td>A narrow line UV–induced non–persistent radical to generate highly polarized transportable glucose solid samples</td>
</tr>
<tr>
<td>10:25-11:00</td>
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<td>COFFEE</td>
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<td>11:00-11:20</td>
<td>T4</td>
<td>Yifan Quan (PSI, CH)</td>
<td>Transportable hydrogen solid state nuclear polarization</td>
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<td>11:20-11:40</td>
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<td>Nobuhiro Yanai (Kyushu University, JP)</td>
<td>Triplet DNP of nanoporous metal–organic frameworks</td>
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<tr>
<td>11:40-12:15</td>
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<td>Arnaud Comment (University of Cambridge, UK)</td>
<td>Developing novel methods for metabolic imaging by hyperpolarized $^{13}$C MR</td>
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<td>12:15-13:45</td>
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<td>LUNCH</td>
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<td>Time</td>
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<td>13:45–14:20</td>
<td>T7</td>
<td>Tom Wenckebach (PSI, CH)</td>
<td>Dynamic nuclear polarization beyond the high-temperature approximation</td>
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<tr>
<td>14:20–14:40</td>
<td>T8, P33</td>
<td>Christian Bengs (University of Southampton, UK)</td>
<td>Master equation for spin systems far from equilibrium</td>
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<tr>
<td>14:40–15:00</td>
<td>T9, P35</td>
<td>Federica Raimondi (University of Nottingham, UK)</td>
<td>Many-body kinetics of dynamic nuclear polarization by the cross effect</td>
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<tr>
<td>15:00–15:35</td>
<td>T10</td>
<td>Armin Purea (Bruker Biospin, DE)</td>
<td>Augmenting the mm wave field in MAS DNP</td>
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<tr>
<td>15:35–17:00</td>
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<td>17:00–17:45</td>
<td>T11</td>
<td>Leif Schröder (FMP Berlin, DE)</td>
<td>Host Structures and their detection schemes for molecular sensing with reversibly bound xenon</td>
</tr>
<tr>
<td>17:45–18:05</td>
<td>T12, P77</td>
<td>Claudia Zanella (EPFL, CH)</td>
<td>Boosting $^{129}$Xe DNP efficiency using ultrasonic sample mixing and microwave frequency modulation</td>
</tr>
<tr>
<td>18:05–18:25</td>
<td>T13, P7</td>
<td>Alice Radaelli (EPFL, CH)</td>
<td>Probing renal pH using hyperpolarized [1–$^{13}$C]-alaninamide</td>
</tr>
<tr>
<td>19:30</td>
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<td>Fedor Jelezko (University of Ulm, DE)</td>
<td>High sensitivity NMR enabled by diamond colour centers</td>
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<tr>
<td>9:45-10:05</td>
<td>W2 P62</td>
<td>Ashok Ajoy (University of California, Berkeley, US)</td>
<td>Optical $^{13}$C hyperpolarization in powdered diamond</td>
</tr>
<tr>
<td>10:05-10:25</td>
<td>W3 P72</td>
<td>Antoine Garcon (Helmholtz Institute, Mainz, DE)</td>
<td>Dark matter searches via ultralow-field nuclear magnetic resonance (CASPEr)</td>
</tr>
<tr>
<td>10:25-11:00</td>
<td></td>
<td>COFFEE</td>
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</tr>
<tr>
<td>11:00-11:20</td>
<td>W4 P68</td>
<td>Bo Zhang (University of Science and Technology of China, CN)</td>
<td>Mesoscopic magnetic resonance spectroscopy with a remote spin sensor</td>
</tr>
<tr>
<td>11:20-11:40</td>
<td>W5 P75</td>
<td>Peter Rakitzis (IELS–FORTH, Heraklion, GR)</td>
<td>High-density spin-polarized H and D from UV photodissociation, and spin-polarized molecules from IR rovibrational excitation</td>
</tr>
<tr>
<td>11:40-12:15</td>
<td>W6 P79</td>
<td>Peter Blümler (University of Mainz, DE)</td>
<td>Nuclear hyperpolarization of $^3$He in magnetized plasma</td>
</tr>
<tr>
<td>12:15-13:45</td>
<td></td>
<td>LUNCH</td>
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<tr>
<td>Time</td>
<td>Session</td>
<td>Speakers</td>
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<tr>
<td>13:45-14:20</td>
<td>W7</td>
<td>Chair: Marc Baldus (Utrecht University, NL)</td>
<td>Gaël de Paëpe (University of Grenoble, FR)</td>
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<td>Hypersensitivity with DNP: natural isotopic abundance and closed-loop cryogenic He sample spinning</td>
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<tr>
<td>14:20-14:40</td>
<td>W8/P110</td>
<td>Snaedis Björgvinsdóttir (EPFL, CH)</td>
<td>Bulk nuclear hyperpolarization of inorganic solids</td>
</tr>
<tr>
<td>14:40-15:00</td>
<td>W9/P134</td>
<td>J. Ole Brauckmann (Radboud University, NL)</td>
<td>A low–temperature (25K) MAS DNP setup for materials studies</td>
</tr>
<tr>
<td>15:00-15:35</td>
<td>W10</td>
<td>Marek Pruski (Ames Laboratory, Iowa, US)</td>
<td>Advances in atomic–scale characterization of materials surfaces by DNP–enhanced solid–state NMR</td>
</tr>
<tr>
<td>15:35-17:00</td>
<td></td>
<td>TEA and POSTERS</td>
<td></td>
</tr>
<tr>
<td>17:00-17:20</td>
<td>W11/P43</td>
<td>Chair: Marcel Utz (University of Southampton, UK)</td>
<td>Tomas Orlando (MPI Göttingen, DE)</td>
</tr>
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<td>Scalar $^{13}$C–Overhauser DNP in the liquid state at low and high magnetic fields</td>
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<td>17:20-17:40</td>
<td>W12/P123</td>
<td>Alessandra Lucini Paioni (Utrecht University, NL)</td>
<td>Spatial localization and selectivity in dynamic nuclear polarization</td>
</tr>
</tbody>
</table>

19:30 CONFERENCE DINNER
TALKS
Hyperpolarized $^{13}$C MRI: Initial Clinical Applications

Jeremy Gordon$^1$, Peder Larson$^1$, Hsin-Yu Chen$^1$, Natalie Korn$^1$, Robert Bok$^1$, Mark VanCriekinge$^1$, James Slater$^1$, Rahul Aggarwal$^2$, Matt Cooperberg$^2$, Daniel Vigneron$^1$ and John Kurhanewicz$^{1,2}$

$^1$Departments of Radiology and Biomedical Imaging and $^2$Urology, UCSF

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The first-in-human study of hyperpolarized (HP) $^{13}$C MR showed that injection of HP $[\text{\textsuperscript{1-13}C}]$pyruvate was safe and that both 1- and 2-D dynamic and 3D single time-point imaging of HP $[\text{\textsuperscript{1-13}C}]$pyruvate metabolism was feasible (1). Since the completion of this phase 1 clinical trial, a number of significant technical improvements have been made and implemented in on-going patient studies. These include; improved technology and strategies for generating (SpinLab\textsuperscript{TM} polarizer) and delivering HP $[\text{\textsuperscript{1-13}C}]$pyruvate, new MR data acquisition sequences, and multichannel $^{1}$H/$^{13}$C radio frequency RF coils. As a result of these technical improvements, the achievable polarization of $[\text{\textsuperscript{1-13}C}]$pyruvate has more than doubled (from $\approx 18\%$ to $\approx 40\%$), the time to delivery of HP $^{13}$C pyruvate was reduced (from $\approx 68$ sec to $\approx 55$ sec), and 3D dynamic echo planar spectroscopic imaging (EPSI) and spectrally selective echo planar imaging (EPI) sequences have been implemented with increased spatial and temporal resolution relative to the initial clinical trial. Two HP probe injections in a single patient exam has been FDA approved, and while initial patient studies were focused on $[\text{\textsuperscript{1-13}C}]$pyruvate, $[\text{\textsuperscript{2-13}C}]$pyruvate has been FDA approved and is being added to $[\text{\textsuperscript{1-13}C}]$pyruvate in on going clinical trials. Additionally, funded clinical research studies are working towards the use of $^{13}$C urea, and $[\text{\textsuperscript{5-13}C}]$glutamine in combination with $1-^{13}$Cpyruvate in patient studies.

Early patient validation studies involving test-retest reproducibility, correlations with pathologic findings, and clinical outcomes such as survival and disease progression after treatment have been initiated. In a study utilizing 2D dynamic EPSI of pre-prostatectomy prostate cancer patients, time-to-max pyruvate was reproducible when corrected for the arterial input function with no significant difference observed in repeat injections of the same patient (2). A significant increase in the Lactate/Total Carbon ratio was measured cancer vs. normal and in Gleason 3 vs. 4/5 lesions (2). In two recent clinical trials of pre-prostatectomy and patients before and after treatment, a 3D dynamic EPSI sequence was used to obtain full prostate coverage and using an SNR threshold of 14 for HP $[\text{\textsuperscript{1-13}C}]$pyruvate, rate of conversion ($k_{PL}$) maps created and correlated with pathology and multiparametric $^{1}$H MRI. It was found that $k_{\text{plmax}}$ was significantly higher in high-grade (Gleason $\geq 4+3$) prostate cancer versus both normal prostate and low-grade (Gleason $\geq 3+4$) disease. After effective therapy there was a significant early reduction in $k_{\text{plmax}}$ that occurred prior to changes in mp-$^{1}$H MRI (3). HP $^{13}$C MRI has also be used to image cancer metastases to the Live and Bone (4).

DIRECT DETECTION OF GLUCOSE METABOLISM IN VIVO IN HUMAN GBM MICE MODELS BY HYPERPOLARIZED \([^{2}H_{7},^{13}C_{6}]\)GLUCOSE

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\(^{13}\)C MRS of hyperpolarized endogenous compounds via dissolution DNP (dDNP)[1], was shown as a promising technique that is capable to provide metabolic information in real-time, and has been employed to study tumor metabolism in large variety of animal models[2]. Glioblastoma (GBM) are the most malignant primary brain tumor in adults, they exhibit high metabolic activity and are notorious for their resistance to multimodal therapy, with a median survival of only 15 months. Aberrant glucose metabolism is considered a hallmark of cancer, via the so called ‘Warburg Effect’ manifested by the switch of glucose metabolism and ATP production from oxidative phosphorylation to glycolysis, however recent ex vivo studies show evidences for active glucose oxidation in human GBM[3,4]. Direct detection of tumor glycolysis can provide new evidences on this debate. Thus the present work relates to the optimization of hyperpolarized \(^{13}\)C glucose experiment for direct detection of cerebral glycolysis in mice brain[5] and its application in human GBM mice model. To account for the different compartments of the human GBM, measurements were performed on two type of highly aggressive GBM mice models, i.e. U87 tumor that represent the heterogeneous GBM lesion, and LN-3708GS mice model[6] that represent the invisible infiltrative compartment of GBM. We demonstrate the feasibility to detect tumor glycolysis in real time in GBM mice model with hyperpolarized \([^{2}H_{7},^{13}C_{6}]\)glucose. We report that larger amount of hyperpolarized \([1^{13}\)C]lactate is produced in the focal tumor compared to the infiltrative one after the infusion the hyperpolarized \([^{2}H_{7},^{13}C_{6}]\)glucose during our measurement time (ca. 50 s), that may indicate on higher glycolysis rate in the focal tumor compared to the infiltrative one.

First *in cellulo* and *in vivo* metabolic studies using ParaHydrogen Hyperpolarized [1-13C]pyruvate.

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[1-13C]pyruvate hyperpolarized by means of d-DNP has been widely exploited for *in vivo* metabolic imaging studies [1]. Para-hydrogen hyperpolarization of this substrate has been demonstrated through the so called PHIP-SAH method (Figure 1). In the proof-of-concept study [2] several issues (hyperpolarization level, bio-compatibility of product, concentration of HP substrate) had still to be solved in order to make the solution of HP pyruvate obtained through this method suitable for metabolic studies.

In this work [3], the various steps of this method have been investigated in order to find the main experimental parameters whose optimization has to be pursued in order to increase the 13C polarization level on the final product. We report also about the studies that have been carried out to increase the concentration of the product in the water solution and to obtain a bio-compatible aqueous solution of the HP metabolite.

Finally, HP [1-13C]pyruvate thus obtained has been applied in the investigation of the kinetics of the metabolic exchange of the 13C HP label with lactate on different cancer cells and *in vivo*. In the *in vivo* studies, slice-selective 13C-MR spectra have been acquired on mutant mice healthy and tumor-bearing mice using a 1T MRI system.

![Figure 1](image)

**Figure 1.** a) Scheme of the PHIP-SAH procedure: I) esterification of the carboxylate group with an unsaturated alcohol; II) hydrogenation of the unsaturated alcohol with para-enriched hydrogen; III) polarization transfer from the parahydrogen protons to the 13C carboxylate signal; IV) hydrolysis of the ester. The orange arrows indicate that these passages are carried out in an organic solvent, while the blue that the reaction occurs in an aqueous phase. B) series of 13C-NMR spectra acquired after perfusion of HP [1-13C]pyruvate through a suspension of 4T1 breast cancer cells.

References

During the last decade, the development of nuclear spin polarization enhanced (hyperpolarized) molecular probes has opened up new opportunities for studying the inner workings of living cells. The hyperpolarized signal is produced \textit{ex situ} and detected with high sensitivity using high-resolution NMR spectroscopy, Fig.1.A. Experimental investigations of chemical reactions in the cell require quantitative tools for time-resolved \textit{in situ} analyses in physiologically relevant settings. However, dissolution DNP (dDNP)[1] is not, a priori, a quantitative method when applied in studies of complex molecular systems and incomplete description of the signal evolution has until now limited dDNP to an observing tool.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{A. Set-up for studying dDNP hyperpolarised bioprobes in living cells. [2] B. Glycolytic metabolites quantified in breast (MCF7) and prostate (PC3) cancer cells incubated with $^{13}$C$_6$-$d_7$-glucose. [3]}
\end{figure}

The use of dDNP to enhance metabolite extracts benefits from the high sensitivity and resolution provided by hyperpolarized samples in high-field NMR spectrometers, from the possibility to quantify metabolites by comparison with an internal standard, and from the capability to monitor slow metabolic transformations. The obtained metabolic signatures are analysed and compared using metabolomics tools. Biological hypotheses are made using extracts from cancer cells incubated with $^{13}$C$_6$-$d_7$-glucose for many minutes in living cells, Fig.1.B.

Molecular imaging is likely to play an increasingly important role in predicting and detecting tumour responses to treatment and thus in guiding treatment in individual patients [1]. We have been developing methods for detecting the early responses of tumours to therapy, including metabolic imaging with hyperpolarized $^{13}$C-labelled substrates. We have been using this technique to detect tumour treatment response, to monitor disease progression and to investigate the tumour microenvironment (reviewed in [2]).

Exchange of hyperpolarized $^{13}$C label between lactate and pyruvate and net flux of label between glucose and lactate have been shown to decrease following treatment. We have compared the effectiveness of this technique for detecting early evidence of treatment response with similar $^{18}$FDG-PET measurements. Exchange of hyperpolarized $^{13}$C label between injected [1-$^{13}$C]pyruvate and endogenous lactate can also be used to monitor disease progression. In a genetically engineered mouse model of pancreatic cancer we showed increased lactate labelling as the disease progressed, which potentially could be used clinically to guide earlier intervention. We have also used hyperpolarized [1-$^{13}$C]pyruvate to investigate glycolytic metabolism in patient derived xenograft (PDX) models of glioblastoma, which showed significant metabolic heterogeneity between tumours derived from different patients, and to monitor response and resistance to PI3K inhibitors in genetically engineered models of breast cancer. We have shown that the capacity of tumours to resist oxidative stress can be determined by monitoring the reduction of [1-$^{13}$C]dehydroascorbate and by monitoring flux of hyperpolarized $^{13}$C label from glucose into an intermediate in the pentose phosphate pathway. Although hyperpolarization of the $^{13}$C nucleus produces a massive gain in sensitivity further potential gains in sensitivity are possible if the polarization is transferred to adjacent spin-coupled protons in the molecule. We have recently demonstrated the feasibility of this approach by imaging hyperpolarized [1-$^{13}$C]lactate via its methyl protons.

Metabolic imaging with hyperpolarized $^{13}$C-labelled cell substrates has translated to the clinic and we conducted our first clinical study in Cambridge in 2016. Some early results in breast cancer and in glioma will be presented.

Hyperpolarization techniques often suffer from relatively high experimental complexity and fast signal decay. In these regards, Parahydrogen Induced Polarization (PHIP) is highly attractive because parahydrogen is an easy to prepare pure quantum reagent with the ability to directly polarize long-lived singlet states. Of particular interest are recent advances with SABRE (Signal Amplification By Reversible Exchange), which drastically broaden the range of substrates and enable particularly long hyperpolarization lifetimes.\cite{1,2,3} As result, hyperpolarized markers are produced directly in room temperature solutions that can probe slow or complex processes \textit{in vitro} or \textit{in vivo}.

A first step to extend hyperpolarization lifetimes is to hyperpolarize heteronuclei with long $T_1$ (e.g. $^{13}$C, $^{15}$N) instead of protons. This is best achieved inside magnetic shielding. An approach dubbed SABRE-SHEATH (SABRE in SHield Enables Alignment Transfer to Heteronuclei).\cite{4} Mechanism and substrate scope will be discussed.

In order to extend signal lifetimes further, long-lived singlet states are hyperpolarized that relax with a decay time constant $T_S >> T_1$. Examples include $^{15}$N$_2$ pairs on diazirines ($T_S >20$ min; $4 \times T_1$)\cite{1} or $^{13}$C$_2$ pairs in acetylene groups ($T_S > 2$ min; $10 \times T_1$).\cite{5} For increased sensitivity it is also attractive to transfer long-lived hyperpolarization to close-by protons for more sensitive detection. However, moving protons close to long lived singlets typically has detrimental effects on their lifetime. Here, terminal diazirines will be discussed where the high symmetry enables, both, a long lifetime and efficient polarization transfer to $^1$H for detection.

To maximize hyperpolarization levels, we introduce stroboscopically pulsed SABRE-SHEATH experiments. Instead of using a constant low magnetic field in the shields, the low field is only turned on for short time periods ($\sim 22$ ms). This converts the SABRE-typical incoherent polarization transfer into a coherent process and results in more than doubling of hyperpolarization levels. An approach that can be used to maximize magnetization as well as singlet order.

Finally, the combination of SABRE-SHEATH with biorthogonal ligation will be presented.\cite{6} Highly selective reactions of hyperpolarized $^{15}$N$_4$-tetrazines result in both, specifically targeted hyperpolarized adducts as well as $^{15}$N$_2$ \textit{para-nitrogen} gas, which represents an unexplored quantum reagent with potential for very long singlet lifetimes and intriguing applications.

Para-hydrogen Induced Polarization: Over 50% $^1$H and $^{13}$C polarization of metabolite precursors and 12% $^{15}$N polarization with 20 minutes $T_1$ in water

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Para-hydrogen Induced Polarization (PHIP)\textsuperscript{1} is a hyperpolarization technique that utilizes the singlet order of para-hydrogen, which is converted into observable magnetization upon addition to an unsaturated bond. Its applicability to produce biomedical imaging contrast agents has been limited due to the unavailability of unsaturated precursor molecules to which para-hydrogen can be added. Recently, the PHIP – SAH approach was introduced (PHIP by side arm hydrogenation), broadening possibilities for hyperpolarizing metabolites.\textsuperscript{2} In this method, an unsaturated bond is attached at first to a metabolite of interest, the bond hydrogenated with para-enriched hydrogen and the yielded polarization transferred to a $^{13}$C nuclei of interest in a metabolite. Cleavage of the polarized precursor yields the hyperpolarized metabolite. We will present our recently introduced pulsed NMR approach with which nearly unity polarization transfer from $^1$H polarization to $^{13}$C spins can be achieved experimentally.\textsuperscript{3} In optimized side arms linked to 1-$^{13}$C acetate, we have achieved over 50% $^1$H and $^{13}$C polarization within a few seconds polarization time, paving the pathways for biological applications.

Another challenge for the PHIP technique, is the production of clean contrast agents. In most studies, a homogeneous catalyst is utilized for the hydrogenation reaction. Removing this catalyst remains difficult and a desired approach would be to utilize a heterogeneous catalyst that can be filtered after the polarized metabolite has been generated. We have introduced nano-catalysts based on transition metals that can be dispersed in water, yielding high levels of polarization.\textsuperscript{4} Recently, we succeeded in polarizing compounds above $P = 10\%$ (which is considered to be the threshold for in vivo experiments)\textsuperscript{5} with novel designed catalysts that will be presented during the meeting.

Lastly, it would be desirable to introduce molecular probes that can be hyperpolarized and traced in vivo for long times. In the most commonly applied metabolic probe, 1-$^{13}$C pyruvate, the hyperpolarized signal can be monitored up to 3 minutes ($\sim 3T_1$). We have succeeded in hyperpolarizing a $^{15}$N compound with PHIP that possess a longitudinal relaxation time in water of 20 minutes. An average polarization of $P = 12\%$ was achieved by utilizing the aforementioned pulsed approach. Molecular improvements for long-lived tracers will be discussed, giving hope for designing hyperpolarized contrast agents with bio-activity that can be monitored for longer than 30 minutes in vivo.

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Light-Induced hyperpolarization in reversible reactions of biomolecules

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We developed very efficient methods for creating light-induced spin hyperpolarization termed chemically induced dynamic nuclear polarization (CIDNP) [1] that can provide valuable data on the structure and reactivity of short lived radicals in biological systems at ambient conditions not obtainable by standard techniques.

The talk describes significant progress in three directions:
(I) development of hardware and new techniques for investigating hyperpolarization over a wide range of magnetic fields and microsecond time resolution at high field;
(II) development of theory and methodology of spin hyperpolarization in condensed media;
(III) application of spin hyperpolarization to the study of various chemical processes of biologically important molecules.

We continued with the development and application of methods of photo-induced nuclear spin hyperpolarization and relaxation in condensed media extending over a magnetic field range from 5 nT to 10 T. [2] According to our methodological developments, the studies are largely devoted to the application of spin-hyperpolarization methods to the study of reactions and processes involving short-lived radical species. New results were obtained on the study of fast radical reactions involving biologically important molecules, in particular on the structure and reactivity of such radicals. Photoreactions of various benzophenones with biomolecules were studied in detail focused on intra- and intermolecular electron transfer.

CIDNP of the pyrimidine bases of thymine and thymidine DNA was studied in detail. Results on formation and decay of a newly discovered unusual guanosine radical cation including its pH dependence will be presented. [3] An oxidation reaction with the DNA base thymine in the presence of photosensitizers produces other short-lived nucleotide radicals. Here the abovementioned advantages of the CIDNP method will be amplified.

The magnetic field dependence of CIDNP as a source of information about electronic exchange interaction will be shown for a number of promising molecular systems: in recently synthesized dyads, which can be used in photovoltaics, and in biradicals of the flavin-adenine dinucleotide molecule. [4] For signal enhancement methods based on field variation were developed to transfer polarization among protons and heteronuclei, as well as to create "long-lived" polarization of hetero-nuclei as will be illustrated by various examples.

Metal-Free Parahydrogen-Based Hyperpolarized Contrast Agents Produced via Rapid Catalyst Capture

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Hyperpolarization techniques based on the use of parahydrogen provide orders of magnitude signal enhancement for NMR and MRI. The main drawback limiting widespread applicability of parahydrogen-based techniques in biomedicine is the presence of organometallic compounds (the polarization transfer catalysts) in solution with hyperpolarized contrast agents. These catalysts are typically complexes of platinum-group metals and their administration in vivo should be avoided [1-4]. Herein, we show that a rapid (in less than 10 seconds) Ir-based catalyst ([Ir(IMes)H2S3]Cl (1), IMes = 1,3-bis(2,4,6-trimethyl-phenyl)imidazol-2-ylidene; COD = cyclooctadiene, S = pyridine) [5] capture by metal scavenging agents can produce pure parahydrogen-based hyperpolarized contrast agents as demonstrated by high-resolution NMR spectroscopy and inductively coupled plasma atomic emission spectroscopy (ICP-AES). The presented methodology enables fast and efficient means of producing pure hyperpolarized aqueous solutions for biomedical and other uses [6].

Figure 1. a) Chemical structures of metal scavengers used in the SABRE catalyst capturing studies. b) Concentration of Ir detected by ICP-AES after overnight storage of a 0.5 mL aqueous solution of 1 in the presence of different metal scavengers (10 mg). Scavengers’ identification (ID) numbers are listed in Figure 1a. Sample labeled X contained no scavenger. c) Concentration of Ir detected by ICP-AES after rapid capture (<10 s) of 1 from the 0.5 mL aqueous solution by different amount of the added metal scavenger (ID #3). Metal capturing efficiency is shown on the right.

FIELD SWEPT POLARIZATION TRANSFER IN PARAHYDROGEN NMR

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Much work in the field of parahydrogen-enhanced NMR involves the transfer of proton polarization to heteronuclei using the molecular J-coupling network. Techniques such as magnetic field cycling [1] and ‘SABRE-SHEATH’ [2] have emerged for this purpose. Both techniques work by exploiting avoided state crossings at ultra-low magnetic fields.

We present a surprising new discovery: If a molecule containing a heteronuclear spin is parahydrogenated at some magnetic field to yield an AA’X spin system, and the field is adiabatically swept through the zero point and up in the opposite direction, the parahydrogen singlet order is transformed into magnetization on the heteronuclear spin.

To demonstrate this, experiments were performed in a ZULF (zero and ultralow field) NMR chamber (shown in Fig. 1), which afforded precise control over the magnetic fields applied to samples. Firstly, acetylene dicarboxylic acid was parahydrogenated to maleic acid. The field was then swept adiabatically from -2 to +2 $\mu$T to polarize the carbonyl $^{13}$C spin. The sample was then shuttled into a Magritek SpinSolve high field benchtop magnet for direct $^{13}$C detection. The result is shown in Fig. 2, alongside a comparison with a sample that did not undergo the field sweep.

We soon hope to employ this technique to hyperpolarize compounds in a continuous-flow manner.

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\textsuperscript{1}H and \textsuperscript{13}C benchtop NMR spectroscopy with SABRE hyperpolarisation

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Hyperpolarisation holds great promise for integration with benchtop NMR spectrometers, whose relatively low magnetic fields (≤ 2 T) limit both sensitivity and chemical shift dispersion. Here we focus in particular on the signal amplification by reversible exchange (SABRE) and SABRE-Relay approaches, which catalytically transfer spin order from the singlet isomer of H\textsubscript{2}, \textit{para}hydrogen (\textit{p}-H\textsubscript{2}), to target analytes in solution.[1,2] These methods are particularly attractive for compact NMR applications because they generate polarisation quickly (in tens of seconds) and the level of polarisation is independent of the detection field. In addition, the SABRE processes are fully reversible and so polarisation can be renewed upon supply of fresh \textit{p}-H\textsubscript{2}.

In this work we explore the potential for SABRE hyperpolarised benchtop NMR spectroscopy to become a robust analytical tool for applications outside of the typical laboratory environment. \textsuperscript{1}H and \textsuperscript{13}C signal enhancements of several orders of magnitude are demonstrated for a range of analytes and the reproducibility of the SABRE response is explored. SABRE-hyperpolarised 2D NMR is achieved on a benchtop spectrometer using a flow approach, where the hyperpolarisation is renewed between each step of the 2D acquisition. This is exemplified for both homonuclear and heteronuclear correlation experiments including \textsuperscript{1}H-\textsuperscript{1}H COSY and \textsuperscript{1}H-\textsuperscript{13}C HETCOR. The potential for reaction monitoring using hyperpolarised benchtop NMR is also demonstrated. Specifically, single-shot measurements of SABRE hyperpolarisation lifetimes are used to quantitatively monitor the activation of the SABRE catalyst and to differentiate the effects of this chemical transformation from the effects of deuteration of the hyperpolarized analyte.

FROM LASER PHYSICS TO THE PARA-HYDROGEN PUMPED RASER

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In this lecture the synergetic properties of the LASER [1] are compared with the key features of the recently discovered p-H_2 pumped RASER [2] (Radio Frequency Amplification by Stimulated Emission of Radiation). The equations of motion for the LASER can be derived from the slavery principle, i.e. the slowest order parameter (the light field in the resonator) enslaves the rapidly relaxing atomic degrees of freedom. Likewise, the equations of motion for the p-H_2 pumped RASER result from a set of order parameters where the transverse magnetization of the RASER active spin states enslave the electromagnetic modes. This has striking consequences for NMR spectroscopy, since long lasting multi-mode RASER oscillations allow for unprecedented spectroscopic resolution down to the micro-Hertz regime. According to the theory of the multi-mode RASER three different types of operation are predicted: 1. Renormalization, 2. self-organized mode locking and 3. RASER in the NMR mode. Certain RASER experiments involving the protons of 3-picoline or 15N pyridine molecules pumped with the SABRE mechanism [3] show in the time domain either one single RASER oscillation, or self-organized giant RASER pulses or a complex RASER beat pattern. The corresponding 1H spectra consist of one ultra-narrow line at the renormalized frequency, or equidistant narrow lines (frequency comb) or ultra-narrow lines reflecting the NMR properties of the pumped molecule. Numerous applications in the area of material sciences, fundamental physics and medicine involving sensitive magnetic sensors or NMR spectroscopy with ultra-high precision become feasible at low cost.

CONTINUOUS FLOW SABRE POLARIZATION FOR NUCLEAR MAGNETIC RESONANCE AND NUCLEAR SPIN-INDUCED MAGNETO-OPTIC EXPERIMENTS

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Nuclear magneto-optic spectroscopy (NMOS) is a young field of research studying effects based on interaction between nuclear spin magnetization and light radiation mediated by the molecular electron cloud. The simultaneous influence of optical excitations and localized magnetic fields from aligned nuclear spins gives rise to intrinsic, molecule-specific optical responses, such as linear or circular birefringence. While NMOS phenomena are closely related to NMR observables, such as chemical shifts and dipolar couplings, the presence of perturbation by the light also brings in additional information about electronic structure. The only experimentally observed NMOS effect is the so-called nuclear spin-induced optical rotation (NSOR) [1], but the efforts have so-far dealt mostly with pure substances, such as neat solvents, or binary mixtures of compounds, both of which were present in appreciable fractional amounts of tens of percent. In addition to NSOR, several other NMOS phenomena have been theoretically predicted [2], but not experimentally observed. As with the NMR, one of the main experimental concerns is the low spin polarization leading to low sensitivity.

We report a system that uses para-H₂ and SABRE method [3] to produce continuous supply of polarized sample and flow it through the bore of an NMR magnet or NMOS cell for measurements. As a demonstration we present the comparison of NMR spectra of pyridine polarized either thermally or using our setup, showing successful continuous hyperpolarization of the sample and great increase in signal intensity. We also report our findings on the imaging capabilities of the flowing liquids in our system. Furthermore, the combination of a solution-based continuous hyperpolarization technique with the NMOS instrumentation allows observation of NSOR of samples in sub-molar concentrations with the signal quality comparable to that of neat liquids investigated in previous studies, bringing it closer to chemically relevant conditions and significantly widening the pool of viable samples.


Spin Isomer Conversion in Water Endofullerene at Room Temperature

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Molecular endofullerenes consist of a small molecule such as H\textsubscript{2}, H\textsubscript{2}O or HF encapsulated in a cage of carbon atoms, such as C\textsubscript{60}. The molecule is trapped inside the cage but is free to rotate. The H\textsubscript{2} and H\textsubscript{2}O molecules have two distinct spin isomers: ortho and para with total spins of \textsuperscript{1}H nuclei 1 and 0 respectively.

At room temperature the ortho-to-para ratio in H\textsubscript{2}O@C\textsubscript{60} is 3:1, but at low temperatures the equilibrium changes to essentially pure para water. Samples of H\textsubscript{2}\textsuperscript{16}O@C\textsubscript{60} and H\textsubscript{2}\textsuperscript{17}O@C\textsubscript{60} solutions were thermalised at 4.2 K to induce conversion into the para isomer. Then the samples were rapidly transferred into a high-resolution NMR magnet and dissolved in room temperature solvent. The conversion of excess para water to ortho leads to slow increase of \textsuperscript{1}H signal for H\textsubscript{2}\textsuperscript{16}O@C\textsubscript{60}. In H\textsubscript{2}\textsuperscript{17}O@C\textsubscript{60} the conversion gives rise to an antiphase pattern in the \textsuperscript{1}H spectrum which is attributed to quantum-rotor-induced polarization. We estimate time constants for the para-to-ortho conversion at room temperature as $30 \pm 4$ s for H\textsubscript{2}\textsuperscript{16}O@C\textsubscript{60} and $16 \pm 3$ s for H\textsubscript{2}\textsuperscript{17}O@C\textsubscript{60} \cite{1}.

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HYPERPOLARISATION USING THE BRUTE FORCE APPROACH

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We have previously shown that the brute force approach to hyperpolarisation (i.e. exposure to very low temperature and high field), in conjunction with nanoparticle-mediated relaxation enhancement, can yield very high nuclear polarisation on a realistic timescale [1]. We have also shown that the brute force method can be coupled with a dissolution system to yield hyperpolarised molecules in solution, in a similar manner to dissolution-DNP [2]. We have now brought together two low-temperature systems and a high resolution NMR spectrometer in one laboratory so that we can combine developments in relaxation enhancement with optimisation and automation of the sample ejection, dissolution, nanoparticle filtration and subsequent analysis. We will describe these systems for improved automation and reliability, as well as results and remaining challenges for improved enhancement in 1-13C pyruvic acid, both with and without Pt nanoparticles as ultra-low T relaxation agents. In this way we aim to bring the brute force method a step further towards providing a viable alternative and complement to dissolution-DNP and other hyperpolarisation technologies.

SINGLE-SCAN $^{13}$C DIFFUSION-ORDERED NMR SPECTROSCOPY OF DNP-HYPERPOLARISED SUBSTRATES

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The sensitivity of solution-state NMR experiments can be increased by several orders of magnitude with dissolution dynamic nuclear polarization (D-DNP). This hyperpolarisation method is of great potential use for the analysis of low concentrated mixtures of small molecules.1 The amplified polarisation, however, only lasts for a few tens of seconds or less, because of longitudinal relaxation. Diffusion-ordered spectroscopy (DOSY), a method to separate the NMR spectra of components in a mixture, would be useful for the analysis of hyperpolarised mixtures. Conventional DOSY experiments, however, require long experiment duration that are not compatible with D-DNP.

We show that hyperpolarised $^{13}$C DOSY experiments can be recorded in a single scan, using a spatial encoding of the diffusion dimension. A pulse sequence for spatially encoded (SPEN) DOSY is described, based on the work of Keeler and Frydman,2,3 which accelerates experiments by an order of magnitude.4 D-DNP is then used to hyperpolarise a mixture of small molecules, together with SPEN DOSY for the acquisition of a time-series of $^{13}$C DOSY spectra.5 Several modifications are made to the original sequence, in order to compensate for the effect of convection, and to make it possible to acquire a time-series of spectra from a single dissolution experiments. Throughout the analysis, numerical simulations are used, based on a Fokker-Plank formalism to describe simultaneously the spin and spatial dynamics.6 Theses simulations are key to characterise the pulse sequence and derive an improved model to obtain more accurate diffusion coefficients from SPEN DOSY experiments.

Hyperpolarised $^{13}$C DOSY is a promising tool for the monitoring of chemical reactions and the analysis of molecular interactions.

Dynamic Nuclear Polarization (DNP) has recently evolved into a cornerstone technology to overcome the sensitivity limitations of solid-state NMR. This technique, originally developed for low magnetic fields, has been shown to be applicable at high fields, opening new avenues in materials and life sciences. In this presentation we will present results from high field (18.8 T) and fast Magic Angle Spinning (MAS) (~40 kHz) DNP NMR. In particular, we will discuss the introduction of new polarizing agents in which a BDPA (α,γ-bisdiphenylene-β-phenylallyl) moiety and a nitroxide are chemically tethered. We will show that, at very high magnetic field and fast spinning frequency, these hybrid biradicals significantly outperform current reference binitroxides. Applications to the characterization of challenging surfaces will be reported.
In this work we present recent results of site-directed spin labeling on a protein to show the effect of the transition metal Gd(III) as a polarizing agent (PA) on the NMR properties a biological system. Ubiquitin is a small, easy to handle, robust protein. The absence of cysteines allows for specific mutations for site-directed spin labeling. Therefore, ubiquitin is well suited as a biological model system.

We investigate the influence of varying levels of deuteration of ubiquitin on DNP. The results for different nuclei with varying effect on relaxation, enhancement and spin diffusion will be shown. By sweeping the magnetic field the solid effect matching condition can be chosen to specifically hyperpolarize hydrogen, carbon, or nitrogen, revealing large differences between the different nuclear types. While on carbon relatively small but significant enhancement factors on the order of ~10 are observed, this factor is boosted to over 100 on nitrogen. Uniformly across the nuclei build-up times increase for increasing levels of deuteration. Additionally, by comparing linewidths for different polarization periods and deuteration levels, we can follow the expanding range of hyperpolarization by spin diffusion. Finally, we deduce major contributions of this effects to the origin of methyl-induced $^{13}$C relaxation.

Alkaptonuria (AKU) is a rare disease due to a deficiency of homogentisate 1,2-dioxygenase on the tyrosine degradation pathway. Patients have an elevated plasma level of homogentisic acid (HGA) which accumulates over time in collagenous tissues, especially cartilage. HGA can polymerise into a dark pigment, and the darkly pigmented cartilage tissue shows drastic changes in mechanical properties giving rise to severe and early osteoarthritis. It is intriguing to understand how a relatively simple molecule such as HGA can lead to widespread changes in the biomechanical properties in the pigmented cartilage. Thus far, no animal or in vitro model can fully replicate the pigmentation process in the cartilage of human patients.

Using DNP-enhanced solid-state NMR, we carried out our study on human tissue obtained from joint replacement surgery. Pigmented and non-pigmented sections from the same patient were investigated. Using $^1$H-$^{13}$C NMR correlation spectra, we were able to attribute a low level signal in the aromatic region to the pigment species in the degraded cartilage from an AKU patient. Furthermore, hydrogen bond lengths in the collagen triple helix show a different distribution in pigmented cartilage compared to non-pigmented cartilage, indicating disruption to the cartilage extracellular matrix at the level within the collagen triple helix. Our study illustrates the potential of DNP-enhanced solid-state NMR to contribute to the study of biopsies and samples with medical and clinical relevance.
Fifteen years after its invention, dissolution dynamic nuclear polarization (d-DNP)[1] had apparently settled into well-defined technologies and methodologies, and it was mostly believed that d-DNP needed to be performed at the point of use. However recently, a series of advances have shaken foundations of d-DNP. For the first time, it was demonstrated that d-DNP could potentially be performed remotely, off-site,[2] thus without the need of a polarizer.

In our group, we have in the past years, merely been working at improving efficiency,[3] compatibility,[4] and repeatability[5] of d-DNP. Our candid objective basically was to enable (or at least to improve) some applications; nonetheless it has led us to prepare the ground of a new concept i) to dramatically extend hyperpolarization lifetimes from minutes to days and, ii) to enable transport to far distant MRI or NMR sites.[2]

We are now generalizing this new concept to a broad range of systems, such as neat endogenous tracers, mixtures of metabolites, or amino acids, by developing new hyperpolarizing solids such as our silica-based HYPSO materials, or more recently polymer-based porous materials. These can be impregnated with arbitrary solutions that are then hyperpolarized efficiently and stored and transported over hours, before being melted and released. We will in particular present a new epoxy-based polarizing material. We’ll show how the porosity and morphology of this material can be tuned, and we will present DNP results with absolute polarization values exceeding 50% on the very first generation of these new materials.[6]
Sub-second dissolution-DNP at minimal dilution

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In dissolution-DNP, a sample containing hyperpolarized molecules such as pyruvate is dissolved with a jet of hot solvent propelled by helium gas. The solute is then transferred to a target magnet where strongly enhanced signals report structural and dynamic information, such as human metabolic fluxes in tumours [1,2].

D-DNP has great potential also in NMR spectroscopy, but substantial dilution and long transfer times often lead to disappointing results.

We are developing rapid-transfer dissolution-DNP, in which the sample is loaded into a bullet that is shot to the target magnet using pressurized helium gas, within typically 100 ms. A dissolution dock in the target magnet dissolves the sample (typically 50 uL) in 600 to 700 uL of aqueous solvent and reliably loads 5 mm NMR tubes within 700 to 800 ms. Polarization levels of several percent have been observed on 1-13C pyruvate, with a substantial potential for further improvements. We will present a detailed description of our implementation and compare the method to conventional dissolution-DNP.

A narrow line UV-induced non-persistent radical to generate highly polarized transportable glucose solid samples


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Photo-induced radicals, generated via UV-light irradiation of frozen solutions containing a fraction of pyruvic acid (PA), are suitable to perform DNP on several substrates [1, 2]. The unique property of this polarizing agent is its non-persistency: they suffer from thermal stress and they are naturally scavenged if the temperature of the DNP sample is raised above 190 K. This feature has demonstrated a possible way to hyperpolarization storage and transport [3].

In the present work, for the first time, we use as radical precursor a pyruvic acid derivative that is not involved in metabolic pathways: trimethyl pyruvic acid (Tri-PA). Moreover its molecular structure provides a sharper ESR line compared to PA (see Fig A). The latter represents an advantage for DNP of $^{13}$C. The DNP properties of the new radical precursor were tested on glucose, a substrate showing increasing interest among the dDNP community.

Tri-PA was added in concentration of 0.7 M to a solution containing 2 M of [U-2H, U$^{13}$C]glucose dissolved in a mixture H$_2$O:glycerol 1:1 (v/v). Frozen beads of the sample were UV-irradiated in liquid nitrogen for 300 s with a high power (20 W/cm$^2$) broad-band UV source (Dymax BlueWave 75) to generate a radical concentration around 40 mM. DNP was performed using a 6.7 T/1.1 K polarizer. Shining microwaves at optimal conditions (x mW at 188.19 GHz with 20 MHz/1kHz modulation), $^{13}$C was polarized up to 48±2 % in about 1 h (see Fig B). After dissolution and transfer (10 s delay) to a 9.4 T high resolution vertical NMR magnet a polarization of 29±1 % was measured (see Fig C). As comparison, an similar sample containing 30 mM Trityl instead of the UV-radical precursor, was prepared. In this case, 37±2 % $^{13}$C polarization was achieved in the solid state (20±1 % after dissolution). Using the same Trityl radical concentration we can routinely polarize [1-$^{13}$C]PA to 65 – 70 %. The results show that UV-irradiated Tri-PA combine efficient DNP properties to its natural thermal quenching above approx. 190 K, is a valuable and inexpensive polarizing agent for a challenging dDNP substrate such as glucose.

Transportable hydrogen solid state nuclear polarization

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In the methods of dynamic nuclear polarization (DNP), a high polarization of an electron spin system is transferred to the nuclei by means of a microwave field. These very electron spins are however also responsible for the decay of the nuclear polarization via spin lattice relaxation. Using short-lived optically excited triplet states instead of stable radicals as source of electron polarization practically eliminates the main path of nuclear spin lattice relaxation. Using triplet DNP the protons in a pentacene doped naphthalene bulk single crystal have been polarized to a record value of 80% at a field of 0.36 T using a simple helium flow cryostat for cooling. This highly polarized sample has been kept at very moderate conditions of temperature around 80 K and magnetic field of 24 mT and transported to a neutron beam line without loss of polarization, where it served as a spin filter for polarization analysis in a neutron scattering experiment. Furthermore the polarized sample can be extracted from the DNP apparatus and stored and transported in a small holding magnet under liquid nitrogen.
Triplet DNP of nanoporous metal-organic frameworks

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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. In typical scheme of triplet DNP (Fig. 1a), 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 pulsed microwave irradiation for satisfying Hartmann-Hahn condition, so-called integrated solid effect (ISE).

Previous studies of triplet DNP have been limited to solid-state crystalline and amorphous materials, and it remains difficult to hyperpolarize biology-relevant probes. To overcome this limitation, we introduce the chemistry of metal-organic frameworks (MOFs) to the field of triplet DNP (Fig. 1b). The nanoporous structure of MOFs allows the accommodation of polarizing agents as well as other guest molecules. This work paves the way towards the hyperpolarization of various probe molecules at room temperature for imaging applications.

Fig. 1 (a) Typical scheme of Triplet-DNP. (b) Schematic illustration of Triplet-DNP in MOFs accommodating polarizing agents.
Numerous preclinical applications have demonstrated the enormous potential of hyperpolarized $^{13}$C magnetic resonance imaging (MRI) for \textit{in vivo} metabolic imaging and several research hospitals are currently performing studies on patients. To take advantage of this technology, a hyperpolarizer has to be placed in the vicinity of the MRI scanner and the hyperpolarized $^{13}$C-labeled metabolic substrates need to be produced a minute or less prior to the injection. This delay as well as the required synchronization between the production and the injection limits the type and number of \textit{in vivo} metabolic imaging experiments that can be done.

In this lecture, I will present novel methods that open new opportunities to perform hyperpolarized $^{13}$C MRI through the circumvention of some of the limitations of the current hyperpolarization technology. In particular, I will show how dynamic nuclear polarization (DNP) methods based on non-persistent photoinduced radicals can be designed to dramatically increase the lifetime of the hyperpolarized state by increasing the $^{13}$C longitudinal relaxation time of frozen $^{13}$C-molecules [1-3].


In Dynamic Nuclear Polarization (DNP) via the cross effect and thermal mixing the polarization of nuclear spins is a four step process: a microwave field reduces the polarization of electron spins resonant with the microwave frequency. Spectral diffusion transfers this reduced polarization to other electron spins. Triple spin flips of two electron spins and a nuclear spin transforms differences of electron spin polarization into nuclear spin polarization. Finally nuclear spin diffusion transfers this polarization across the sample.

This contribution addresses three long standing issues concerning the first three steps. A correct treatment of the saturation of electron spin polarization and spectral diffusion requires that conservation of energy is obeyed. Such is possible using Provotorov's theory of magnetic resonance saturation and cross relaxation [1] who introduced a non-Zeeman reservoir to collect energy surpluses and replenish energy shortages. However, his theory is restricted to the high temperature approximation, in which Boltzmann factors are expanded linearly. As many applications require such high polarizations that this approximation is not justified, an extension to low temperature is necessary. Recently such extensions were made [2] and these will be shortly reviewed in this contribution.

These newly developed models for magnetic resonance saturation and spectral diffusion serve as a basis for the solution of a long standing duality in the treatment of triple spin flips: the 'cross-effect' approach based on second order perturbation theory [3,4], versus the semi-classical 'thermal mixing' approach [5,6], which thus far was moreover limited to the high temperature approximation.

This contribution proposes an alternative approach, in which the mixing of electron spin states by their mutual interaction is calculated exactly, and next the super-hyperfine interaction is considered to flip the nuclear spins. It extends the treatment to low temperature, and unifies the two earlier approaches: the 'cross-effect' approach and 'thermal mixing' approach are just two different limiting cases.

An analysis of energy flows and of the evolution of spin temperatures answers issues that could not be understood thus far, or were explained by stop-gap explanations like 'leakage'. It explains e.g. why different nuclear spin species may still end up having the same spin temperature, even when spectral diffusion is slow, so the microwave field burns a hole in the electron spin resonance (ESR) spectrum. Transfer of the method to other processes having such dual theoretical approaches—e.g. direct nuclear spin-lattice relaxation—is also conceivable.

The recent developments in Magnetic Resonance clearly indicate an increasing interest in hyperpolarization techniques. Dynamic Nuclear Polarization (DNP), quantum rotor induced polarization (QRIP) and para-hydrogen induced polarization (PHIP) allow for the study of previously inaccessible systems. Polarization levels greatly exceed thermal Zeeman polarization and the spin-systems are far from equilibrium. As a consequence relaxation processes will equilibrate the spin-system with its environment.

Within the NMR community relaxation phenomena are often described by semi-classical relaxation theories [1]. The drawback of the semi-classical approach is that it cannot account for finite temperatures of the environment. The spin-system would therefore relax towards a non-physical equilibrium state. To correct for this misbehaviour a class of thermalization techniques have been developed [2, 3].

Recently we were able to report para-to-ortho conversion of water at room temperatures by means of rapid dissolution-DNP for the first time [4]. Description of the relaxation dynamics by means of conventional thermalization procedures led to wrong results. In general conventional thermalization procedures are not well-suited for spin-systems far from equilibrium.

We now propose a new thermalization technique which faithfully describes relaxation dynamics of spin-states far from equilibrium and generates the correct thermal state. The intuition behind our approach is based on the stochastic wave function approach [5]. Theoretical considerations are complemented by SpinDynamica simulations of simple model systems.

Many-body Kinetics of Dynamic Nuclear Polarization by the Cross Effect

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Dynamic Nuclear Polarisation (DNP) provides significant signal enhancement compared to conventional thermal polarisation techniques used in typical nuclear magnetic resonance applications. Of the possible DNP mechanisms, the cross effect (CE), involving triple spin-flips between two interacting electrons and a nucleus, is most efficient at low temperatures and microwave irradiation amplitude. In silico optimisation of parameters affecting CE enhancement, such as radical concentration or biradical design, require simulation of large spin systems. However, the computational expense of solving the Liouville-von Neumann equation for such systems makes this approach intractable after only a few spins. Here we show that the non-equilibrium nuclear polarization build-up is effectively driven by three spin incoherent Markovian dissipative processes. These processes can be modelled using a classical kinetic Monte Carlo simulation algorithm, giving us favourable scaling of simulation time with system size. With our theoretical approach, we have been able to simulate a system of over 100 spins, allowing for the first time the study of many-body processes such as spin diffusion.

Augmenting the mm wave field in MAS DNP

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In MAS DNP, polarizing spins of unpaired electrons is generally performed by shining a mm wave beam onto an MAS rotor. DNP performance depends on the electron B_1 field in the sample, apart from other factors such as radical type and concentration. Numerical analysis using commercial software is a suitable method for studying the electromagnetic fields that are obtained inside the stator, rotor and sample, such as initially presented by Nanni et al. [1] and more recently by Golota et al. [2].

Using such methodology as a design tool, we have optimized the irradiation schemes for 3.2mm and 1.3mm MAS systems at 263GHz. Starting from average B_1 fields of about 0.56 MHz/√W (20 μT/√W) in the sample, we have achieved 1.0 MHz/√W (37 μT/√W) at 3.2mm using a combination of sapphire lens, concave mirror and optimized rotor wall. With a related design for 1.3mm DNP, the field was increased to about 1.8 MHz/√W (65 μT/√W). Both designs have been validated by DNP experiments, resulting in a reduction of required power and higher enhancement.

The DNP enhancement can also be increased by adding dielectric particles to the sample, as shown by Kubicki et al. [3]. This effect can likewise be attributed to an increased B_1 field. We have further investigated the particle effect by analyzing its dependence on particle size, input beam polarization and variability of dielectric particle distributions. Extending from our previous methodology of looking at frequency domain monitors following a pulse excitation, we have studied the actual time evolution following cw irradiation, resembling the experimental case. Thus we were able to study the resonant properties of samples with and without particles. Numerical simulations are again supplemented by DNP experiments.

Figure 1: B_1 field at 263GHz inside 3.2mm MAS stator, central cut perpendicular to the rotor axis; (left) 3.2mm standard, (right) 3.2mm optimized

HOST STRUCTURES AND THEIR DETECTION SCHEMES FOR MOLECULAR SENSING WITH REVERSIBLY BOUND XENON

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Reversibly bound xenon can be explored through chemical exchange saturation transfer (CEST) measurements[1] for various sensing applications that involve targeted Xe hosts or competitive host-guest complex formation. This approach has proven to increase the sensitivity for NMR and MRI of so-called functionalized \( ^{129}\text{Xe} \) by several orders of magnitude. The original detection scheme focuses on the transient binding of only Xe and has been tested for different host structures, both of synthetic and of biological origin.

We have demonstrated different strategies for controlled, efficient knock-out of the hyperpolarization with CEST protocols and used this for targeting various cell surface markers, including glycans and claudins.[2,3] A further sensitivity enhancement can be achieved by switching to multivalent hosts that incorporate \( 10^2-10^3 \) Xe atoms.[4,5] A recent expansion of the CEST concept focuses on molecular containers that can bind alternative guests beside Xe. The sensing approach then relies on the Xe displacement by such competitive guests to alter the net saturation transfer and/or to cause an observable change in \( T_2 \) relaxation of unbound Xe.[6]

This talk will give an overview of different approaches pursued in our lab using cryptophanes, hollow protein structures, and cucurbit[n]urils (n = 6, 7) for NMR and MRI applications with hyperpolarized \( ^{129}\text{Xe} \). The latter type also allows for time-resolved studies on enzymatic activity when combined with accelerated CEST encoding schemes. Overall, reversibly bound Xe nowadays offers various detection options for sensing of different analytes beyond the classic Hyper-CEST scheme and continues to expand the set of high-sensitivity tools for diagnostic purposes.

The unique properties of Hyperpolarized (HP) $^{129}$Xe provide a highly sensitive tool for probing the local environment. HP $^{129}$Xe has been extensively used to study materials or for biomedical MRI including functional imaging of the human lung or brain [1][2]. Alternatively to the well-established hyperpolarization method Spin Exchange Optical Pumping (SEOP), sublimation-DNP offers the advantage of employing non-dedicated hardware and perspectives of potentially higher throughput [3,4]. Nevertheless, the challenges of homogeneously embedding solid $^{129}$Xe into a radical-doped glassing matrix [5] and the consequently lower nuclear polarization levels achieved prevented sublimation-DNP from spreading across the hyperpolarization community. In the present work we propose an improved sample preparation and the use of microwave modulation to enhance DNP performances in a system characterized by poor electron spin spectral diffusion [6].

Sample homogeneity was improved by using ultra-sonication instead of magnetic stirring. All measurements were performed at 5 T and 1.5 K on a sample containing 5M Xe dissolved in 50 mM TEMPO-doped isobutanol. The microwave irradiation frequency was set to 139.9 GHz, which corresponds to the maximum positive DNP enhancement.

Modulating the output frequency of the microwave source (ELVA-1 VCOM-06/140/1/50-DD) by means of a sinusoidal function showed a strong dependence of the DNP performances on the sinusoid’s amplitude (see Fig. 1, modulation frequency fixed at 10 kHz). In optimal conditions (44 MHz modulation amplitude) the enhancement was improved by a factor 2.5. Furthermore, the build-up time was reduced by 25% independent of the modulation amplitude. Moreover, the new sample preparation procedure employing ultrasonic waves guaranteed more reproducible results and further increased the polarization levels achieved.

PROBING RENAL PH USING HYPERPOLARIZED [1-\textsuperscript{13}C]ALANINAMIDE

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Hyperpolarized molecular probes can be effectively used as pH markers. To date, the only two probes reported \textit{in vivo} as extracellular pH sensors are \textsuperscript{13}C- bicarbonate [1], and \textsuperscript{[1,5-\textsuperscript{13}C\textsubscript{2}]}zymonic acid [2],[3]. Alaninamide [4, 5] is a derivative of alanine which is found to be sensitive to variations of pH in the physiological range. The aim of the present study was to assess the feasibility of using alaninamide as a pH probe \textit{in vivo}.

The alaninamide titration curve was determined by performing \textsuperscript{13}C NMR measurements at 9.4 T, 37° on a set of 500 mM Ala-NH\textsubscript{2} HCl samples of varying pH referenced to \textsuperscript{13}C urea. \textsuperscript{[1-\textsuperscript{13}C]}Alaninamide was polarized at 1 K in a 7 T polarizer, then rapidly dissolved in a buffered solution and injected IV into a Sprague Dawley rat (n=6) located in a 9.4 T animal scanner. \textsuperscript{13}C FIDs were acquired with 30° BIR4 pulses using a single loop \textsuperscript{1}H / quadrature \textsuperscript{13}C surface coil placed over the left kidney. The pH was perturbed by injecting acetazolamide IV (10 mg/kg) one hour prior to infusion.

The alaninamide titration curve shows a \textsuperscript{13}C\textsubscript{1} chemical shift change of \approx 8.4 ppm, and a pK\textsubscript{a} of 7.9. The pH sensitivity of \textsuperscript{13}C\textsubscript{1} results in three distinct alaninamide spectral peaks, corresponding to three different extracellular pH compartments within the kidney (pH = 7.46, pH = 7.22, pH = 6.58) that can be tentatively assigned to the cortex/blood, medulla and calyx/ureter. With acetazolamide treatment, the pH in the first compartment follows the change in pH of the blood, while the pH in the third compartment does not reflect the urine pH and shifts during the brief experiment. No change is observed in the pH value of the second compartment.

High sensitivity NMR enabled by diamond colour centers

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The sensitivity of magnetic resonance depends strongly on nuclear spin polarisation. Therefore, significant effort was directed towards the development of protocols for enhancing nuclear spin polarisation above the thermal value. Dynamic nuclear polarisation protocols that use polarisation transfer from electron spins to nuclear spins have been realised and their application in imaging has been demonstrated recently. However, the polarisation transfer reaches its best performance at low temperatures where electron spins are strongly polarised in thermal equilibrium. Here we demonstrate an efficient scheme that realises optically induced $^{13}C$ nuclear spin hyperpolarisation in diamond at room temperature and low ambient magnetic field. Optical pumping of a nitrogen-vacancy center creates a continuously renewable electron spin polarisation, which can be transferred to surrounding $^{13}C$ nuclear spins. We will also discuss recent results diamond based polarisation of external to diamond nuclear spins.
OPTICAL $^{13}$C HYPERPOLARIZATION IN POWDERED DIAMOND

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Nitrogen Vacancy (NV) centers in diamond are an attractive platform for dynamic nuclear polarization of nuclear spins, particular because they are electronic spins can be optically polarized at room temperature with modest laser powers. In the quest towards NV driven DNP, nanodiamond powder is particularly attractive: they have huge surface areas (>6700 mm$^2$/mg for 100nm particles), and one could arrange for a close physical contact between the polarized NVs and external nuclear spins.

Indeed the goal of optically "hyperpolarized nanodiamonds" has been a long-standing one; yet the strong orientational dependence of the spin-1 NV centers has remained challenging to surmount.

In this work, we overcome these challenges to optically hyperpolarize diamond powder, obtaining high bulk $^{13}$C polarization (>0.25%) comparable to the best results in single crystals [1]. We have developed a new, remarkably simple, low-field optical DNP technique that proves to be fully orientation independent. Our technique also allows simple control of the hyperpolarization direction, which only depends on the direction of microwave sweeps across the electron spectrum [2].

We have constructed a low-cost, portable, table-top micro-diamond "hyperpolarizer" that is capable of hyperpolarizing 5um diamond particles. The device also opens up several avenues for harnessing the biocompatible surface-functionalized nanodiamonds as MRI tracers.

Dark matter searches via ultralow-field nuclear magnetic resonance (CASPER)

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The nature of dark matter, the invisible substance that makes up over 4/5 of the matter in the universe, is one of the most intriguing mysteries of modern physics. Elucidating the nature of dark matter would profoundly impact our understanding of cosmology and particle physics.

Recent theories of couplings between dark matter and nuclear spins have opened the possibility of directly detecting axion, axion-like and dark-photon dark matter via NMR spectroscopy [1]: as nuclear spins move through the galactic dark-matter halo, the spins couple to dark-matter particles and behave as if they were in an oscillating magnetic field, potentially generating a dark-matter-driven NMR signal. The Cosmic Axion Spin Precession Experiment (CASPER) is multi-faceted NMR search for such particles [2]. Here, we will review a CASPER experiment based on zero- to ultralow-field NMR (ZULF NMR).

We first review the physical principles enabling the detection of dark-matter via ZULF NMR and introduce the off-resonance-based measurement scheme used for such detection. We then describe the current ZULF NMR apparatus and present an exotic data processing scheme, which enables the possibility to perform coherent averaging of transient NMR signals induced by sources of unknown frequencies such as dark matter. Finally we show how recent NMR hyperpolarization schemes such as parahydrogen-induced hyperpolarization and signal amplification by reversible exchange will allow this experiment to probe uncharted territories, digging deeper in physics beyond the Standard Model.

Mesoscopic magnetic resonance spectroscopy with a remote spin sensor

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As one of the most important techniques, magnetic resonance spectroscopy finds broad applications in chemistry, biology and material science. Nanoscale magnetic resonance based on optical detection of electron spin resonance of nitrogen-vacancy (NV) centers in diamond has recently received broad attention in the context of quantum sensing. Magnetic resonance spectroscopy with nanoscale organic samples [1-3] and single molecules [4, 5] have been realized. Until now, the majority of nanoscale experiments measured a statistical fluctuation magnetization of spins which is much stronger than the mean thermal magnetization \( M_z \overset{\approx}{=} \frac{B_0}{T} \) with a nano-detection volume under the ambient conditions with the magnetic field of several hundred gauss. However, the fluctuation signal reduces dramatically with increased distance between the NV sensor and the sample.

For the mesoscale quantum sensing, e.g., cellular-sized magnetic resonance, the thermal polarization magnetization is stronger than the fluctuation. Additionally, higher polarization can be achieved via hyperpolarization approaches such as optically induced polarization [6], dynamic nuclear polarization (DNP) [7-9], and quantum-rotor-induced polarization [10, 11]. The polarization signal can be dominant once the spin polarization $P$ is reasonably high (normally, $P \approx 10^{-2}$ for electron spins and $\sim 10^{-4}$ for nuclear spins) even for the nanoscale sensing.

Here we report a long-range sensing method by detecting the spin polarization, so that mesoscale sensing based on NV center can be realized. This spin polarization removes the power law dependence on the separation distance between the target ensemble and the NV sensor. To demonstrate the method, we detect the mean magnetic field created by optically polarized electron spins within a pentacene-doped crystal. The optically induced polarization is improved a thousandfold compared to the calculated thermal polarization at ~500 G. This results in three orders of magnitude signal enhancement. With this method, we can detect the magnetic resonance spectra and measure its two typical decay times of the pentacene molecules doped in a crystal with the size of a few tens of micrometers. The long-range sensing method paves the way for mesoscopic quantum sensing in chemistry, biology and material science at ambient conditions.

I describe two novel methods for the production of spin-polarized atoms and molecules, through the UV and IR optical excitation of molecules:

First, the UV photodissociation of hydrogen-isotope halides (e.g. HCl, Dl), with circularly polarized light, can produce, at first, highly electron-spin-polarized H/D atoms [1,2,3,4]. Subsequently, the electron polarization is transferred to the nuclei and back via the hyperfine interaction, in ~1 ns. We measure these hyperfine quantum beats of the electron magnetization using a pick-up coil, for pulsed H and D densities of ~10^{19} cm^{-3} [5], which is about 6 orders of magnitude higher than those produced by conventional continuous-production Stern-Gerlach or optical-pumping methods. We characterize the depolarization, through a DI-D intermediate species, which helps explain the unusually long polarization lifetime of ~10 ns and the saturation of the depolarization rate at high pressures. I discuss proposals, based on this method, for measuring polarized laser fusion of D-T, D-3He, and D-D reactions [4], and for producing spin-polarized molecules through chemical reactions.

Second, the IR rovibrational pulsed-excitation of molecules, with circularly polarized light, followed by the hyperfine interaction, produces spin-polarized nuclei, after an optimal time delay, typically on the μs time scale [6,7,8,9]. The nuclear polarization can be isolated in the nuclei, by terminating the hyperfine beating, either by photodissociating the molecules or trapping them at surfaces.

Nuclear Hyper-polarization of $^3$He in Magnetized Plasma

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The nuclear spins of $^3$He can be hyper-polarized at high magnetic fields (4.7 T) solely by a magnetized plasma, i.e. without any LASERs being involved. The conditions for such a magnetized plasma are fulfilled when the mean free collision path is much larger than the gyration radius of the free electrons in the gas discharge.

The induced atomic orientation results in absolute polarization levels of up to 10%. We explain this phenomenon by an alignment-to-orientation mechanism in the excited $^3P$-state of $^3$He which is most efficient when the Zeeman and the spin-orbit energies are comparable.

Magnetometry at high magnetic fields [1,2] will obviously benefit from the PAMP-effect (Polarized Atoms from Magnetized Plasma), because the experiment can be compacted or even miniaturized due to dispensable optical components. Here a relative precision of $10^{-12}$ is demonstrated. The limits of the methodology are discussed in view of relative [1] and absolute determinations of magnetic fields.


“Hypersensitivity with Dynamic Nuclear Polarization: natural isotopic abundance and closed-loop cryogenic helium sample spinning”

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In this presentation, we will first describe our efforts towards rationalizing MAS-DNP efficiency, notably by investigating NMR off-signal losses occurring during MAS-DNP experiments.[1-2] Specifically we will compare the (MAS-dependent) depolarization effect for several “gold-standard” (bi-)radicals currently in use in most DNP studies (e.g. Totapol/bTbK/Amupol/TEMTriPol/etc.). Finally we will show that MAS-DNP simulations can be used to rationalize these observations [1,3] and design new and improved polarizing agents. The AsymPol family will be introduced.

In order to further enhance the sensitivity, we will report on a strategy to push the limits of DNP-enhanced solid-state NMR beyond its current state-of-the-art. This leap-forward was made possible thanks to the employment of a closed-loop of cryogenic helium as the gas to power magic angle sample spinning (MAS) for DNP-enhanced NMR experiments. The experimental conditions reported here far exceed what is currently possible and allows reaching sample temperatures down to 30 K while conducting experiments with high spinning frequencies (up to 25 kHz @ 100 K for a 3.2 mm probe). Thanks to the impressive associated gains, which will be presented, sustainable cryogenic helium sample spinning significantly enlarges the realm and possibilities of the MAS-DNP technique and is the route to transform NMR into a versatile and sensitive atomic-level characterization tool.[4]

Finally we will report on our strategy towards solving structure of organic assemblies. The ability to record correlation experiments for nuclei at low natural isotopic abundance (13C, 15N) using dynamic nuclear polarization (DNP) [5,6] shows great promise for the field of NMR crystallography. The low natural abundance statistically simplifies coupled systems to spin pairs, making the measurement of inter-nuclear distances (through dipolar recoupling experiments) more straightforward. Examples will be shown on natural isotopic abundance self-assembled systems, such as peptides and guanosine derivatives, where π-stacking interactions and hydrogen-bonding were probed.[6,7] Finally, we will show that NMR dipolar buildups can be used (in combination with the unit cell dimensions) to perform de novo crystal structure determination of small molecules.

MAS DNP can be used to hyperpolarize the bulk of organic solids, given that spontaneous $^1\text{H}-^1\text{H}$ spin diffusion transports magnetization generated at the surface into the particle. We report a strategy for hyperpolarizing inorganic proton-free materials, using incipient wetness impregnation and spin diffusion among heteronuclei. Multiple cross-polarization contacts are used to transfer hyperpolarization from protons in a radical containing wetting phase to heteronuclei at the surface of the material. Provided that heteronuclear T$_1$ values are long, even slow spin diffusion from surface to bulk can result in spectra with better sensitivity than is obtained with conventional solid-state NMR. We show how a factor 50 gain in overall sensitivity of the $^{119}\text{Sn}$ spectrum of SnO$_2$ can be achieved using this method. Spin diffusion is also observed among $^{31}\text{P}$ nuclei in GaP, $^{113}\text{Cd}$ in CdTe and $^{29}\text{Si}$ in SiO$_2$ ($\alpha$-quartz).

Figure 1. Left: DNP enhanced CP-MAS $^{119}\text{Sn}$ spectra of SnO$_2$ impregnated with 16 mM TEKPoI in tetrachloroethane, showing spin diffusion among tin nuclei. Right: Schematic representation of hyperpolarization of proton-free inorganic bulk.
A LOW TEMPERATURE (25K) MAS DNP SETUP FOR MATERIALS STUDIES

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In this contribution we present our first results with a low temperature MAS DNP NMR setup operating at 600 MHz / 395 GHz. The system consists of a Varian NMR system combined with a 395 GHz Bruker gyrotron that is coupled quasi-optically to a Tycko design Revolution 4 mm MAS DNP NMR probehead, allowing spinning of approximately 8 kHz at temperatures down to 25K. We will present details of the setup and show that, despite the fact that the system is still under development, the sensitivity obtained for natural abundant \(^{13}\text{C}\) spectra is very competitive in terms of sensitivity per unit time for polymeric materials.

As a first application we show a study of aramid finishes; polyaramid fibers have superior mechanical properties but are chemically almost inert. To incorporate these fibers into composite materials, such as tires, an activation finish is required for improved adhesion between the fibers and the rubbery-matrix of the composite material. The mechanism of this reinforcement is still under debate.

In order to study the finish and its interaction with the aramids by \(^{13}\text{C}\) and \(^{15}\text{N}\) NMR spectroscopy we need to overcome the challenges of the low concentration of the finish (1%-wt) in combination with the low natural abundance of the isotopes under study. Therefore, we selectively enhance the sensitivity at the interface by a DNP protocol by a matrix-free approach to incorporate stable DNP-biradicals into the finish material. We show that good DNP enhancements (\(\varepsilon>60\)) are obtained using this approach which allows us to selectively study the interface region of the composite polymer system. Based on the high sensitivity of this protocol (\(^{13}\text{C}\) SNR~4500 in a single scan), we explore which \(^{13}\text{C}-^{13}\text{C}\) DQ-SQ experiments are optimal for the moderate spinning speeds available under the conditions described above. We demonstrate that \(^{13}\text{C}-^{13}\text{C}\) correlation spectra are within reach for these challenging heterogeneous samples and discuss the implications of the chemistry we observe for the adhesion model in these composite materials.
The developments in dynamic nuclear polarization (DNP) made during the last two decades have boosted solid-state (SS)NMR’s sensitivity far beyond the conventional limits. We will present several recent examples from our laboratory of applications of this technology to the studies of surfaces and interfaces of materials. Indirect or direct DNP measurements of $^{17}$O lineshapes, $^1$H-$^{17}$O distances, and 2D $^1$H-$^{17}$O spectra were used to understand the acidity and dynamics of OH groups and observe the support-metal interactions in a series of heterogeneous catalysts. The structures of surface-bound catalytic metal centers and associated ligands were determined by DNP-enhanced $^{195}$Pt, $^{89}$Y, $^1$H, $^{13}$C, $^{15}$N, and $^{29}$Si SSNMR spectra. Two-dimensional DNP-based $^{29}$Si-$^{29}$Si and $^{13}$C-$^{13}$C homonuclear correlation SSNMR spectra were used to characterize the spatial distributions of functional groups attached to the surfaces of mesoporous materials. Finally, we used DNP-enhanced $^{13}$C-$^{27}$Al, $^{29}$Si-$^{27}$Al and 3D $^1$H-$^{17}$O-dipolar correlation experiments to elucidate the coordination geometries of the substrates at the alumina surface and atom ordering in amorphous silica-alumina materials.
SCALAR $^{13}\text{C}$-OVERHAUSER DNP IN THE LIQUID STATE AT LOW AND HIGH MAGNETIC FIELDS

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DNP in liquids is driven by electron-nuclear cross-relaxation, known as Overhauser effect (O-DNP). In the past, enhancements of < $10^2$ were observed at room temperature at high magnetic fields (>1 T) on $^1\text{H}$ nuclei [1], due to the strong field dependence of dipolar relaxation. However, we recently reported $^{13}\text{C}$ O-DNP enhancements at 3.4 T of three orders of magnitude [2], which were dominated by scalar hyperfine relaxation.

Here, we present an extension of this study to different magnetic fields on two model systems, i.e. CCl$_4$ and CHCl$_3$, doped with nitroxide radical (TEMPONE) as polarizing agent. Accurate determination of Overhauser parameters allowed us to disclose the primary role of the scalar hyperfine interaction to the $^{13}\text{C}$ nuclei as mediated by either chlorine atoms or protons.

Experimental measurements performed at 1.2, 9, and 14 Tesla allowed us to complete the characterization of the polarization transfer efficiency, represented by the coupling factor, over a broad frequency range. Such field dependence can be successfully described by the subtle combination of dipolar and scalar relaxation.

Furthermore, a proper choice of polarizer can also be the key to optimize the efficiency of scalar O-DNP. Indeed, fullerene-nitroxide derivatives [3] are superior to TEMPONE radical at low fields, displaying at 1.2 Tesla a positive enhancement of ~800 in $^{13}\text{CCl}_4$, about 1.5 times larger than the one obtained with TEMPONE. Our results show the potential of O-DNP as a tool to address $^{13}\text{C}$-NMR sensitivity issues at different fields.

SPATIAL LOCALIZATION AND SELECTIVITY in DYNAMIC NUCLEAR POLARIZATION

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In recent years, Dynamic Nuclear Polarization (DNP) has become a powerful tool for structural studies [1][2], with applications spanning from the solid-state NMR studies of proteins [1][3], to the development of heterogeneous catalysts [4][5]. However, despite its current widespread use, important questions remain unanswered regarding the exact location as well as polarization transfer specificity of a DNP radical for given macromolecular systems.

In our contribution we examine the influence of molecular size and proton density upon the resulting DNP efficiency and spatial polarization transfer specificity. We make use of AMUPol [6] as well as a taggable version thereof (AMUPol_MTSSL) we had introduced earlier [7]. We compare our experimental findings to theoretical studies using a classical spin diffusion approximation [8-10] as well as quantum-mechanical multi-electron-nuclear spin system calculations [11]. Finally, we introduce a novel approach to spatially localize DNP radicals in a macromolecular system.

Time Domain Dynamic Nuclear Polarization
(and some CW experiments on proteins)

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This presentation will selectively cover closely related sets of experiments that employ time domain and continuous wave (CW) dynamic nuclear polarization (DNP) experiments, magic angle spinning (MAS) NMR, and the application of these techniques to structural determination of amyloid fibrils from Aβ and membrane proteins.

High field dynamic nuclear polarization (DNP) experiments utilizing subterahertz microwaves (~150-600 GHz) are now well established as a routine means to enhance nuclear spin polarization and sensitivity in MAS NMR experiments. Specifically, irradiation of electron-nuclear transitions transfers the large electron polarization from the polarization agent to nuclear spins via the Overhauser effect (OE), the cross effect (CE) and/or the solid effect (SE). However, the field/frequency dependence of the CE and SE enhancements scale as $\omega_0^{-n}$, where n=1-2, leading to attenuated enhancements in experiments at 14.1 and 18.8 T. Accordingly, we have initiated time domain DNP in order to circumvent the field dependence of CW DNP. We show that spin locking the electrons and matching the NOVEL condition serves as an effective approach to time domain DNP, and that the spin lock can be modulated to increase the efficiency of the polarization transfer. In addition, a significant reduction in the power required to perform pulsed DNP is achieved by using the integrated solid effect and sweeping the microwave frequency with an AWG. Finally, we report a new low power approach -- Time Optimized Pulsed DNP (TOP DNP) – that utilizes pulses at $\omega_{0.5}$ synchronized with $\omega_0$, the nuclear Larmor frequency. Time permitting applications to Aβ1-42 and bR will be presented.
POSTERS
## POSTERS

<table>
<thead>
<tr>
<th>number</th>
<th>presenter</th>
<th>title</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Felix Kreis</td>
<td>B1-insensitive partial hyperpolarization transfer in [2,13C]pyruvate</td>
</tr>
<tr>
<td>P2</td>
<td>Justin Lau</td>
<td>A 3D Hybrid-shot spiral for hyperpolarized 13C imaging (3D-HYSS)</td>
</tr>
<tr>
<td>P3</td>
<td>Leslie Mazuel</td>
<td>[1-13C]glutamate hyperpolarisation for metabolism study in the rodent brain using magnetic resonance spectroscopy (MRS)</td>
</tr>
<tr>
<td>P4</td>
<td>Jack Miller</td>
<td>In vivo characterisation and synthesis of hyperpolarized [2,2-3H2,1,3-13C2]acetoacetate</td>
</tr>
<tr>
<td>P5</td>
<td>Mor Mishkovsky</td>
<td>Direct detection of glucose metabolism in vivo In human GBM mice models by hyperpolarized [2H2,13C6]glucose</td>
</tr>
<tr>
<td>P6</td>
<td>Thanh Phong Lê</td>
<td>Probing real-time metabolism and neuroprotection of hyperpolarized L-[1-13C]-lactate in a mouse model of stroke</td>
</tr>
<tr>
<td>P7</td>
<td>Alice Radaelli</td>
<td>Probing renal pH using hyperpolarized [1-13C]alaninamide</td>
</tr>
<tr>
<td>P8</td>
<td>Yoichi Takakusagi</td>
<td>Hyperpolarized [1-13C]pyruvate MRS reveals increased aerobic glycolysis in the ultra-early phase of PSA-negative prostate carcinogenesis</td>
</tr>
<tr>
<td>P9</td>
<td>Hikari Yoshihara</td>
<td>Renal metabolism of hyperpolarized [1-13C]aspartate</td>
</tr>
<tr>
<td>P10</td>
<td>Emmanuelle Flatt</td>
<td>Exploring the potential of hyperpolarized 6Li to study lithium bio-distribution in the rat brain</td>
</tr>
<tr>
<td>P11</td>
<td>Anne Frahm</td>
<td>Analysis of dDNP NMR metabolic data from cancer cells</td>
</tr>
<tr>
<td>P13</td>
<td>Jeremy Gordon</td>
<td>Hyperpolarized 13C MRI of the human brain</td>
</tr>
<tr>
<td>P14</td>
<td>Magnus Karlsson</td>
<td>Hyperpolarized 133Cs ions for investigating membrane impairment in cells</td>
</tr>
<tr>
<td>P15</td>
<td>Olivier Cala</td>
<td>Interaction studies with secondary-labelled hyperpolarized ligands</td>
</tr>
<tr>
<td>P16</td>
<td>Martin Grasheie</td>
<td>pH-Dependency of the spin-lattice relaxation constant (T1) of 13C-labelled hyperpolarized biomolecules</td>
</tr>
<tr>
<td>P17</td>
<td>Filippo Caracciolo</td>
<td>Dynamic nuclear polarization of 13C and 1H β-cyclodextrins</td>
</tr>
<tr>
<td>P18</td>
<td>Théo El Darai</td>
<td>Generating persistent hyperpolarization with porous polarizing polymers</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P19</td>
<td>Arianna Ferrari</td>
<td>Counterintuitive design of non-structured-HYbrid Polarisng Solids for dynamic nuclear polarization</td>
</tr>
<tr>
<td>P20</td>
<td>Sami Jannin</td>
<td>Microwave-gated dissolution dynamic nuclear polarization</td>
</tr>
<tr>
<td>P21</td>
<td>Lionel Arn</td>
<td>Boosting the dynamical nuclear polarization of [1,13C]butyrate with microwave frequency modulation</td>
</tr>
<tr>
<td>P22</td>
<td>Pernille Rose Jensen</td>
<td>Stable isotope-resolved analysis with quantitative dDNP</td>
</tr>
<tr>
<td>P23</td>
<td>Mohammed Albannay</td>
<td>Low microwave attenuation and low thermal loss waveguides for dDNP probes</td>
</tr>
<tr>
<td>P24</td>
<td>Mohammed Albannay</td>
<td>Versatile polarizer NMR spectrometer</td>
</tr>
<tr>
<td>P25</td>
<td>Morgan Ceillier</td>
<td>High-performance fluid-path for dissolution-DNP</td>
</tr>
<tr>
<td>P26</td>
<td>Tian Cheng</td>
<td>Refrigerated-bath cryostat for dissolution dynamic nuclear polarization</td>
</tr>
<tr>
<td>P27</td>
<td>Behdad Aghelnejad</td>
<td>Hyperfine EPR spectroscopy of nitroxides in DNP-water-glycerol mixtures reveals clustering of radicals</td>
</tr>
<tr>
<td>P28</td>
<td>Behdad Aghelnejad</td>
<td>Transferring frozen hyperpolarized droplets for dissolution DNP</td>
</tr>
<tr>
<td>P29</td>
<td>Benno Meier</td>
<td>Sub-second dissolution-DNP at minimal dilution</td>
</tr>
<tr>
<td>P30</td>
<td>James Eills</td>
<td>Application of bullet-DNP to produce long-lived hyperpolarized fumarate</td>
</tr>
<tr>
<td>P31</td>
<td>George Bacanu</td>
<td>Towards quantum-rotor-induced polarization in CH4@C60, methane-endofullerene complex</td>
</tr>
<tr>
<td>P32</td>
<td>Karel Kouřil</td>
<td>Spin-isomer conversion in water-endofullerene at room temperature</td>
</tr>
<tr>
<td>P33</td>
<td>Christian Bengs</td>
<td>Master-equation for spin systems far from equilibrium</td>
</tr>
<tr>
<td>P34</td>
<td>James MacDonald</td>
<td>Hyperpolarisation using the brute force approach</td>
</tr>
<tr>
<td>P35</td>
<td>Federica Raimondi</td>
<td>Many-body kinetics of dynamic nuclear polarization by the cross effect</td>
</tr>
<tr>
<td>P36</td>
<td>Krishnendu Kundu</td>
<td>Electron spectral diffusion and DNP – simulations and experiments</td>
</tr>
<tr>
<td>P37</td>
<td>Takayuki Kumada</td>
<td>Proton hyperpolarization for polarized neutron scattering</td>
</tr>
<tr>
<td>P38</td>
<td>Danhua Dai</td>
<td>Experimental access to the microwave saturation factor at 9.4 Tesla DNP in liquid state</td>
</tr>
<tr>
<td>P39</td>
<td>Vasyl Denysenkov</td>
<td>Compact DNP polarizer for MRI Applications at 1.5 T</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P40</td>
<td>Thierry Dubroca</td>
<td>High enhancement and large volume overhauser liquid DNP at 14.1 T</td>
</tr>
<tr>
<td>P41</td>
<td>Raphael Kircher</td>
<td>Dynamic nuclear polarization enables NMR reaction/process monitoring in the fast flow regime</td>
</tr>
<tr>
<td>P42</td>
<td>Raphael Kircher</td>
<td>Fighting the lifetime issue of NMR hyperpolarisation</td>
</tr>
<tr>
<td>P43 W11</td>
<td>Tomas Orlando</td>
<td>Scalar $^{13}$C-Overhauser DNP in the liquid state at low and high magnetic fields</td>
</tr>
<tr>
<td>P44</td>
<td>Lynda Brown</td>
<td>Synthesis of molecules in pursuit of long lived nuclear singlet states</td>
</tr>
<tr>
<td>P45</td>
<td>Stuart Elliott</td>
<td>Field-cycling long-lived-state NMR of $^{15}$N$_2$ spin pairs</td>
</tr>
<tr>
<td>P46</td>
<td>Mohamed Sabha</td>
<td>Ab Initio computational modelling of singlet relaxation times using Gaussian and Mathematica</td>
</tr>
<tr>
<td>P47</td>
<td>Shinsuke Sando</td>
<td>Design of long-lived hyperpolarized molecular probes and applications</td>
</tr>
<tr>
<td>P48</td>
<td>Manvendra Sharma</td>
<td>High-performance modular probe assemblies for microfluidic nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>P49</td>
<td>Frederike Euchner</td>
<td>Comparison of the hyperpolarization of different fluorinated aromatic systems via photo-CIDNP</td>
</tr>
<tr>
<td>P50</td>
<td>Lars Kuhn</td>
<td>Hyperpolarization-enhanced 2D NMR observation of protein folding In real time</td>
</tr>
<tr>
<td>P51</td>
<td>Patrick Kurle</td>
<td>Photo-CIDNP and recovery studies on tryptophan-labelled aureochrome LOV</td>
</tr>
<tr>
<td>P52</td>
<td>Christopher Wedge</td>
<td>Exploiting radical triplet pair hyperpolarization for sensitivity enhancement in solution state NMR</td>
</tr>
<tr>
<td>P53 M3</td>
<td>Alexandra Yurkovskaya</td>
<td>Light-Induced hyperpolarization in reversible reactions of biomolecules</td>
</tr>
<tr>
<td>P54</td>
<td>Saket Patel</td>
<td>Development of UV-induced non-persistent radicals for dissolution dynamic nuclear polarization</td>
</tr>
<tr>
<td>P55 T3</td>
<td>Andrea Capozzi</td>
<td>A narrow line UV-induced non-persistent radical to generate highly polarized transportable glucose solid samples</td>
</tr>
<tr>
<td>P56</td>
<td>Saiya Fujiwara</td>
<td>DNP of metal-organic frameworks using photo-excited triplet electrons</td>
</tr>
<tr>
<td>P57</td>
<td>Adam Gaunt</td>
<td>Photo-generated radicals on nitroso derivatives for dissolution DNP</td>
</tr>
<tr>
<td>P58</td>
<td>Irene Marco-Rius</td>
<td>Non-persistent, photo-generated radicals for high-yield DNP</td>
</tr>
<tr>
<td>P59</td>
<td>Akinori Kagawa</td>
<td>Room temperature hyperpolarization of equal mixtures of benzoic acid and other aromatic carboxylic acid</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P60 T4</td>
<td>Yifan Quan</td>
<td>Transportable hydrogen solid state nuclear polarization</td>
</tr>
<tr>
<td>P61</td>
<td>Kenichiro Tateishi</td>
<td>DNP with photo-excited triplet electron using soluble pentacene derivatives</td>
</tr>
<tr>
<td>P62 W2</td>
<td>Ashok Ajoy</td>
<td>Optical $^{13}$C hyperpolarization In powdered diamond</td>
</tr>
<tr>
<td>P63</td>
<td>Koichiro Miyamichi</td>
<td>Long-lived state of four-spin system hyperpolarized at room temperature</td>
</tr>
<tr>
<td>P64</td>
<td>Maosen Guo</td>
<td>Nanoscale magnetic resonance imaging of intracellular proteins</td>
</tr>
<tr>
<td>P65</td>
<td>Rui Li</td>
<td>Wide-band microwave magnetometry using a nitrogen vacancy center in diamond</td>
</tr>
<tr>
<td>P66</td>
<td>Murari Soundararajan</td>
<td>100-Fold $^{13}$C DNP Enhancement in diamond nanopowder at 9 T</td>
</tr>
<tr>
<td>P67</td>
<td>Grzegorz Kwiatkowski</td>
<td>Exploiting endogenous paramagnetic surface defects for the direct dynamic nuclear polarization of micro/ nanocrystals of silicon and diamonds</td>
</tr>
<tr>
<td>P68 W4</td>
<td>Bo Zhang</td>
<td>Mesoscopic magnetic resonance spectroscopy with a remote spin sensor</td>
</tr>
<tr>
<td>P69</td>
<td>Jeong Hyun Shim</td>
<td>Hyperpolarization of nanodiamonds at 0.32 T and 3.3 K</td>
</tr>
<tr>
<td>P70</td>
<td>Jeong Hyun Shim</td>
<td>Overhauser dynamic nuclear polarization at nearly zero magnetic field</td>
</tr>
<tr>
<td>P71</td>
<td>Fazhan Shi</td>
<td>Electron spin resonance spectroscopy of a single molecule</td>
</tr>
<tr>
<td>P72 W3</td>
<td>Antoine Garcon</td>
<td>Dark matter searches via ultralow-field nuclear magnetic resonance (CASPER)</td>
</tr>
<tr>
<td>P73</td>
<td>Takeshi Inoue</td>
<td>Development of an optical magnetometer toward highly sensitive magnetometry</td>
</tr>
<tr>
<td>P74</td>
<td>G Rajalakshmi</td>
<td>Development of a Rb optical magnetometer for low-field NMR studies</td>
</tr>
<tr>
<td>P75 W5</td>
<td>Peter Rakitzis</td>
<td>High-density spin-polarized H and D from UV photodissociation, and spin-polarized molecules from IR rovibrational excitation</td>
</tr>
<tr>
<td>P76</td>
<td>Jean-Noel Hyacinth</td>
<td>LOD-ESR investigation of trityl-doped $^{129}$Xe DNP samples at 6.7 T and 1.1 K</td>
</tr>
<tr>
<td>P77 T12</td>
<td>Claudia Zanella</td>
<td>Boosting $^{129}$Xe DNP efficiency using ultrasonic sample mixing and microwave frequency modulation</td>
</tr>
<tr>
<td>P78</td>
<td>Jonathan Birchall</td>
<td>Understanding Rb And Cs spin-exchange optical pumping for application to hyperpolarised $^{129}$Xe functional lung imaging</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P79 W6</td>
<td>Peter Blümler</td>
<td>Method for fast, efficient and continuous application of hyperpolarized $^{129}$Xe in aqueous and biocompatible liquids</td>
</tr>
<tr>
<td>P80</td>
<td>Thomas Meersmann</td>
<td>$^{129}$Xe relaxation, flow, and dispersion studies in catalytic reactors</td>
</tr>
<tr>
<td>P81</td>
<td>Lutosława Mikowska</td>
<td>$^3$He and $^{129}$Xe polarizers for medical applications</td>
</tr>
<tr>
<td>P82 S3</td>
<td>Eleonora Cavallari</td>
<td>First in cellulo and in vivo metabolic studies using parahydrogen hyperpolarized [1-$^{13}$C]pyruvate</td>
</tr>
<tr>
<td>P83 M4</td>
<td>Danila Barskiy</td>
<td>Metal-free parahydrogen-based hyperpolarized contrast agents produced via rapid catalyst capture</td>
</tr>
<tr>
<td>P84</td>
<td>Bernhard Bluemich</td>
<td>Continuous hyperpolarization with parahydrogen in a membrane reactor</td>
</tr>
<tr>
<td>P85 M5</td>
<td>James Eills</td>
<td>Field-swept polarization transfer in parahydrogen NMR</td>
</tr>
<tr>
<td>P86</td>
<td>Anne Friebel</td>
<td>Signal-enhanced medium-field NMR Spectroscopy By parahydrogen induced polarization (PHIP)</td>
</tr>
<tr>
<td>P87</td>
<td>Dariusz Gofowicz</td>
<td>Time-resolved NUS interleaved acquisition on benchtop spectrometer under PHIP condition in a continuous-flow system</td>
</tr>
<tr>
<td>P88</td>
<td>Boyd Goodson</td>
<td>From cleavable “double agents” to polarized targets: New systems and approaches for SABRE and SEOP hyperpolarization</td>
</tr>
<tr>
<td>P89</td>
<td>William Hale</td>
<td>PHIP on a CHIP – hyperpolarisation in microfluidic NMR</td>
</tr>
<tr>
<td>P90</td>
<td>Julia Hollenbach</td>
<td>Carbenes - a novel group of molecules for the metal free activation of parahydrogen?</td>
</tr>
<tr>
<td>P91</td>
<td>Julia Hollenbach</td>
<td>Hyperpolarisation on Tap – towards the construction of a continuous-flow polariser for the production of hyperpolarised metabolites</td>
</tr>
<tr>
<td>P92</td>
<td>Gaspard Huber</td>
<td>Ultrafast 2D NMR analysis of SABRE-hyperpolarised mixtures</td>
</tr>
<tr>
<td>P93</td>
<td>Konstantin Ivanov</td>
<td>Anti-phase spin order of $\text{H}_2$ in high-field experiments with parahydrogen and its manifestations in SABRE-derived polarization</td>
</tr>
<tr>
<td>P94</td>
<td>Sergey Korchak</td>
<td>Over 60% $^{13}$C polarization by pulsed parahydrogen-induced polarization and sidearm hydrogenation</td>
</tr>
<tr>
<td>P95</td>
<td>Hana Kouřilová</td>
<td>Towards PHIP-hyperpolarized $1$-$^{13}$C-pyruvate</td>
</tr>
<tr>
<td>P96</td>
<td>Salvatore Mamone</td>
<td>A pulsed PHIP approach for hyperpolarizing metabolites</td>
</tr>
<tr>
<td>P97</td>
<td>Otto Mankinen</td>
<td>Hyperpolarized ultrafast Laplace NMR</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P98</td>
<td>Andrey Pravdivtsev</td>
<td>Refocused And Double Refocused Only Parahydrogen Spectroscopy (ROPSYz AND DROPSYd)</td>
</tr>
<tr>
<td>P99</td>
<td>Oleg Salnikov</td>
<td>$^{13}$C parahydrogen-induced polarization of acetates and pyruvates</td>
</tr>
<tr>
<td>P100</td>
<td>Stephan Knecht</td>
<td>Kinetics of spin order in SABRE systems at high-fields</td>
</tr>
<tr>
<td>P101</td>
<td>Jennifer Lewis</td>
<td>$^{19}$F hyperpolarisation by Signal Amplification By Reversible Exchange</td>
</tr>
<tr>
<td>P102</td>
<td>Adam Mames</td>
<td>Capabilities and limitations of oligopeptides NMR Signal Amplification By Reversible Exchange</td>
</tr>
<tr>
<td>P103</td>
<td>Ryan Mewis</td>
<td>Forensic hyperpolarization: detecting fentanyl and its pyridyl analogues</td>
</tr>
<tr>
<td>P104</td>
<td>Markus Plaumann</td>
<td>SABRE-based hyperpolarization and substituent effects</td>
</tr>
<tr>
<td>P105</td>
<td>Thomas Robertson</td>
<td>Heterogeneous SABRE catalyst deactivation with resultant $T_1$ lengthening of the analyte</td>
</tr>
<tr>
<td>P106</td>
<td>Emma Stanbury</td>
<td>Quantifying the effect of substrate-iridium binding potential via pKa on SABRE hyperpolarisation</td>
</tr>
<tr>
<td>P107</td>
<td>Marco Tessari</td>
<td>Quantitative NMR analysis at nanomolar concentrations via Para-Hydrogen Induced Hyperpolarization</td>
</tr>
<tr>
<td>P108</td>
<td>Ewoud Vaneckhaute</td>
<td>Cyclic coherent hyperpolarisation of water with $\text{pH}_2$</td>
</tr>
<tr>
<td>P109</td>
<td>Anu Kantola</td>
<td>Continuous-flow SABRE polarization for nuclear magnetic resonance and nuclear spin-induced magneto-optic experiments</td>
</tr>
<tr>
<td>P110</td>
<td>Snaedis Björgvinsdöttr</td>
<td>Bulk nuclear hyperpolarization of inorganic solids</td>
</tr>
<tr>
<td>P111</td>
<td>Frédéric Blanc</td>
<td>Solids DNP of insensitive nuclei and challenging materials</td>
</tr>
<tr>
<td>P112</td>
<td>Olivier Lafon</td>
<td>DNP-NMR of dissolved organic matter and bio-inspired heterogeneous catalysts</td>
</tr>
<tr>
<td>P113</td>
<td>Subhradip Paul</td>
<td>Dynamic nuclear polarisation enhanced solid-state NMR studies of catalytic materials and small organic molecules</td>
</tr>
<tr>
<td>P114</td>
<td>Arthur Pinon</td>
<td>Structure of core-shell nanoparticles determined by relayed DNP NMR</td>
</tr>
<tr>
<td>P115</td>
<td>Philipp Schleker</td>
<td>Surface structural study of N-doped hydrothermal carbon (N-HTC) by isotopic enrichment and DNP-SENS (Dynamic Nuclear Polarization Surface-Enhanced NMR Spectroscopy)</td>
</tr>
<tr>
<td>P116</td>
<td>Daphna Shimon</td>
<td>Dynamic nuclear polarization of Si microparticles using structural defects</td>
</tr>
<tr>
<td>P117</td>
<td>Pierre Thureau</td>
<td>Investigating small particles of organic powders using MAS dynamic nuclear polarization</td>
</tr>
<tr>
<td>number</td>
<td>presenter</td>
<td>title</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>P118 M14</td>
<td>Wing Ying Chow</td>
<td>DNP-Enhanced solid-state NMR enables observation of collagen triple helix structural change in human Alkaptonuria cartilage</td>
</tr>
<tr>
<td>P119</td>
<td>Galia Debelouchina</td>
<td>DNP polarization agents for the cellular milieu: new chemistries and approaches</td>
</tr>
<tr>
<td>P120</td>
<td>Thomas Deo</td>
<td>Structural studies of amyloid-beta interacting with cell membrane using magic-angle spinning DNP</td>
</tr>
<tr>
<td>P121</td>
<td>Henri Heise</td>
<td>Conformational ensembles of disordered proteins: A glimpse into chaos at high sensitivity</td>
</tr>
<tr>
<td>P122</td>
<td>Vojče Kocman</td>
<td>High-resolution structures of multiple folds adopted by GGGAGCG repeat rich oligonucleotides</td>
</tr>
<tr>
<td>P123 W12</td>
<td>Alessandra Lucini Paioni</td>
<td>Spatial localization and selectivity in dynamic nuclear polarization</td>
</tr>
<tr>
<td>P124</td>
<td>Philip Williamson</td>
<td>Proton detected magic-angle spinning dynamic nuclear polarization NMR for the analysis of natural abundance biopolymers</td>
</tr>
<tr>
<td>P125</td>
<td>Claudia Avalos</td>
<td>$^{19}$F Solid-state dynamic nuclear polarization enhanced NMR</td>
</tr>
<tr>
<td>P126 M13</td>
<td>Jörg Heiliger</td>
<td>Site-directed spin labeling of partially and fully deuterated proteins with Gd(III) for site-selective MAS DNP</td>
</tr>
<tr>
<td>P127</td>
<td>Moreno Lelli</td>
<td>Efficient solid-state DNP at high field, fast MAS and high temperature: narrow-line radicals and the role of spin diffusion</td>
</tr>
<tr>
<td>P128</td>
<td>Alicia Lund</td>
<td>Tuning electronic spin properties of BDPA-nitrooxide biradicals for efficient cross effect DNP at magnetic fields up to 21.1 T</td>
</tr>
<tr>
<td>P129</td>
<td>Sucharita Mandal</td>
<td>Synthesis of BDPA radicals and investigation of their stability</td>
</tr>
<tr>
<td>P130</td>
<td>Guinevere Mathies</td>
<td>The conformation of bis-nitrooxide polarizing agents by multi-frequency EPR spectroscopy</td>
</tr>
<tr>
<td>P131</td>
<td>Olivier Ouari</td>
<td>DNP-enhanced SSNMR sensitivity: Improved polarizing agents for high fields</td>
</tr>
<tr>
<td>P132</td>
<td>Svetlana Pylaeva</td>
<td>Electronic structure of BDPA radical in connection to OE-DNP</td>
</tr>
<tr>
<td>P133</td>
<td>Gabriele Stevanato</td>
<td>An efficient Gd$^{3+}$ based complex for high field Dynamic Nuclear Polarization</td>
</tr>
<tr>
<td>P134 W9</td>
<td>Ole Brauckermann</td>
<td>A low temperature (25K) MAS DNP setup for materials studies</td>
</tr>
<tr>
<td>P135</td>
<td>Ivan Sergeyev</td>
<td>263 GHz klystron: A lower-cost route to dynamic nuclear polarization</td>
</tr>
<tr>
<td>P136</td>
<td>Thorsten Maly</td>
<td>DNP NMR spectroscopy using a 263 GHz integrated THz system</td>
</tr>
</tbody>
</table>
B1 INSENSITIVE PARTIAL HYPERPOLARIZATION TRANSFER IN [2-13C]PYRUVATE

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There are advantages in detecting 13C hyperpolarization via spin coupled protons, including a significant increase in SNR compared to direct 13C detection. The published methods for polarization transfer in vivo have the limitation that they deplete 100% of the hyperpolarization of the observed metabolite [1,2]. Here we show, by simulation and experiment, that hyperpolarization can be transferred piecemeal in [2-13C]pyruvate using a pulse sequence that is tolerant of experimental imperfections.

The pulse sequence (Fig. 1A) is based on the BINEPT sequence [3], modified for partial transfer [4]. In one acquisition ~10% of the 2-13C hyperpolarization is transferred into the methyl protons. The methyl proton polarization (3 PH) divided by the depleted 13C polarization (1-PC) at the end of the sequence describes the efficiency of polarization transfer. This value has been simulated in SpinDynamica [5] for a range of 13C excitation frequency offsets and 13C transmitter powers (Fig. 1B). For a phantom imaging experiment, VAPOR water suppression and an EPI readout were added to the sequence. The images (Fig 1C), which were acquired on a Agilent 7T spectrometer using a home-made 1H/13C transmit/receive surface coil, were collected every second after injection of 1 ml hyperpolarized [2-13C]pyruvic acid into a water filled phantom.

The simulations show that, for a large parameter range, full polarization transfer efficiency is preserved. The signal intensity of the images decreases by ~ 30-40% from image to image, which shows successful partial polarization transfer. We hope to apply this sequence soon to in vivo imaging.

A 3D HYBRID-SHOT SPIRAL FOR HYPERPOLARIZED $^{13}$C IMAGING (3D-HYSS)

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A spiral encoding trajectory was used in the first demonstration of hyperpolarized $^{13}$C imaging in the human heart [1]. Spiral-out trajectories are SNR efficient, but for a given FOV, the achievable resolution is limited by readout duration, constrained by $T_2^*$. Multi-shot spirals retain greater signal at higher spatial frequencies by shortening the readout length at the expense of temporal resolution. In this work, a hybrid-shot sampling regime is proposed in which the centre of k-space is obtained using a single-shot trajectory, transitioning to multi-shot at higher spatial frequencies. An image can be reconstructed from the single-shot portion of every time point acquired at a desired temporal resolution. By combining data within an adaptive time window, higher resolution images can be generated at lower temporal resolution.

The iterative Hargreaves algorithm [2] was modified to generate hybrid-shot spiral trajectories. On a Varian 7T preclinical scanner ($G_{\text{max}} \approx 200 \text{ mT/m, } S_{\text{max}} \approx 800 \text{ mT/m/ms}$), an orange was imaged in $^1$H with a single-shot 5 mm in-plane resolution transitioning to 3 shots extending the nominal resolution to 2 mm (Fig 1).

On a Siemens Tim Trio 3T clinical scanner ($G_{\text{max}} \approx 40 \text{ mT/m, } S_{\text{max}} \approx 200 \text{ mT/m/ms}$), a perfused pig liver was injected with 6.25 mmol of hyperpolarized [1-$^{13}$C] pyruvate and imaged using 10 cm $^{13}$C T/R loop coil following spectral-spatial excitation at a temporal resolution of 1.6 s per 3D volume. The hybrid-shot trajectory was designed with single-shot 10 mm in-plane resolution transitioning to 3 shots for nominal in-plane resolution of 5 mm every 4.8 s (Fig 2). Future work will use this trajectory to perform adaptive spatio-temporal resolution imaging of the human heart.


Glutamate hyperpolarisation for metabolism study in the rodent brain using Magnetic Resonance Spectroscopy (MRS)

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Previous studies using MRS showed a change in neurotransmitters levels in the striatum in Parkinson’s disease models, especially glutamate and glutamine[1][2]. However, experimental times are on the order of several tens of minutes. Thus, the aim of this study was to hyperpolarize the [1-13C] glutamate, inject it in vivo and visualise its biodistribution and metabolism inside the rat brain overcoming the challenge of crossing the blood-brain-barrier (BBB).

All experiments were performed on a 3T MR750 scanner (GEHC Milwaukee, WI, USA), using a dual-tuned birdcage coil (1H/13C). Rats were anaesthetized with isoflurane. L-[1-13C]-glutamic acid was hyperpolarized[3] using the Hypersense (Oxford Instruments). The frozen sample was dissolved with buffer then 0.2mL of 9mM hyperpolarized [1-13C] Glutamate solution was quickly administered via the carotid artery. To obtain an osmotic BBB disruption, rats were infused with a hypertonic solution of 25% mannitol. 13C CSI was performed using Spectral-Spatial (SPSP) excitation combined with a single shot spiral readout[4]. Data were acquired from a single transversal slice (20mm) through the brain with FOV=50mm; repetition time=1s; FA=15°. Acquisition was repeated under 1min and started simultaneously with intra-arterial injection. Data reconstruction was performed using MATLAB.

L-[1-13C]-glutamic acid was polarized by up to 15.8% in the liquid state and the T1 was 19.75s. Spectra acquired following injection of hyperpolarized glutamate showed the hyperpolarized 13C-labeled carboxyl bolus, which typically occurred in the carotid after 4s (figure 1). After NaCl infusion, signal was concentrated around the injection site for all the experimental time. With 25% mannitol infusion, the signal was detected in the rat brain after 8s (figures 1 and 2).

In conclusion, the hyperpolarized [1-13C] Glutamate is imaged in vivo in the rat brain. Thus it may be a promising substrate for evaluation of cerebral glutamate activity in conjunction with neurodegenerative disease.

Ketone body metabolism is altered in pathophysiology. Previous work has observed metabolism in hyperpolarised sodium acetoacetate, but it spontaneously decarboxylates in the liquid state with a half life of approximately 30 minutes at pH 7. Consequently, labelled impurities are typically present at concentrations comparable to downstream metabolites following its injection in vivo. Additionally, the reported T1 of [1-13C]acetoacetate is comparatively short (30 s at 7T) with limiting polarisation of 7-8%. [1,2] Here we use a simple synthetic route to Li+[2,2-2H2,1,3-13C2]acetoacetate that is feasible for preclinical imaging and obtains ~20% polarisation with a liquid-state T1 of 76±3 s. Briefly, ethyl-[1,3-13C2]acetoacetate was hydrolysed via LiOD/D2O at 40ºC followed by rotary evaporation, lyophilisation and purification via methanol/ether recrystallisation, with deuteration provided by ketone/enol tautomerization, with a yield of >65%. For DNP, 30 mg aliquots were mixed with 4.8 μL of a 20 mM EPA/10 mM dotarem mixture, neutralised in D2SO4, and frozen as 15 μL spheres in liquid N2 prior to hyperpolarisation at 3.35 T. Dissolution was performed with PBS buffered D2O with an equimolar quantity of 12-crown-4 ether as a lithium chelator (product pH≈7) prior to 1 mL injection into either a phantom or fasted Wistar rats. Cardiac slab-selective spectra were obtained. Plasma lithium and blood ketone concentrations were not significantly increased post injection. In contrast to Na+[1-13C]acetoacetate, we found that Li+[2,2-2H2,1,3-13C2]acetoacetate had no visible impurity peaks (Fig. A) and a more than doubled liquid state T1 (Fig. B). In vivo, the double-labelling resulted in an increased incorporation into visible downstream metabolites. To quantitatively explain the increased solid state polarisation obtained with deuteration, which is not consistent with other reports [4], the thermal mixing model of Serra et al [3] was solved numerically in Mathematica. It was found that the increase in the solid-state nuclear T1 provided by deuteration was insufficient to explain the enhanced polarisation obtained. We therefore believe that as deuteration increases the heat load for the electronic dipolar system to cool additional processes must dominate.

13C MRS of hyperpolarized endogenous compounds via dissolution DNP (dDNP)[1], was shown as a promising technique that is capable to provide metabolic information in real-time, and has been employed to study tumor metabolism in large variety of animal models[2]. Glioblastoma (GBM) are the most malignant primary brain tumor in adults, they exhibit high metabolic activity and are notorious for their resistance to multimodal therapy, with a median survival of only 15 months. Aberrant glucose metabolism is considered a hallmark of cancer, via the so called ‘Warburg Effect’ manifested by the switch of glucose metabolism and ATP production from oxidative phosphorylation to glycolysis, however recent ex vivo studies show evidences for active glucose oxidation in human GBM[3,4]. Direct detection of tumor glycolysis can provide new evidences on this debate. Thus the present work relates to the optimization of hyperpolarized 13C glucose experiment for direct detection of cerebral glycolysis in mice brain[5] and its application in human GBM mice model. To account for the different compartments of the human GBM, measurements were performed on two type of highly aggressive GBM mice models, i.e. U87 tumor that represent the heterogeneous GBM lesion, and LN-3708GS mice model[6] that represent the invisible infiltrative compartment of GBM. We demonstrate the feasibility to detect tumor glycolysis in real time in GBM mice model with hyperpolarized [2H7,13C6]glucose. We report that larger amount of hyperpolarized [1-13C]lactate is produced in the focal tumor compared to the infiltrative one after the infusion the hyperpolarized [2H7,13C6]glucose during our measurement time (ca. 50 s), that may indicate on higher glycolysis rate in the focal tumor compared to the infiltrative one.

PROBING REAL-TIME METABOLISM AND NEUROPROTECTION OF HYPERPOLARIZED L-[1-13C]-LACTATE IN A MOUSE MODEL OF STROKE

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Lactate is known as a neuroprotectant in a mouse middle cerebral artery occlusion (MCAO) model of stroke [1]. It is suggested that it could either provide energy to the deprived neurons, or activate the HCA1 receptor [2]. Magnetic resonance spectroscopy (MRS) with 13C hyperpolarized (HP) lactate allows its real time in-vivo detection, as well as the analysis of its metabolism [3].

The feasibility of probing HP lactate to pyruvate turnover in MCAO after injection of HP lactate was previously assessed [4]. In the present work, a new HP lactate sample providing higher MR signal aims to probe its metabolism more in detail, by not only detecting the turnover of lactate into pyruvate, but also by probing the conversion of the latter into bicarbonate and alanine.

A frozen sample of L-[1-13C]-Lactate doped with OX63 radical was hyperpolarized by dynamic nuclear polarization at 7T/1K. Transient stroke was induced in C57BL6/J male mice by inserting a silicon-coated filament into the middle cerebral artery and withdrawing after 30 min for reperfusion. The animal was then placed into a 9.4T MRI scanner. At 1h or 2h after reperfusion, 325μL of 0.1M HP lactate solution were injected intravenously and immediately followed by 13C MRS acquisitions of the brain every 3s.

Preliminary results of this on-going work suggest that the SNR is sufficient to follow the evolution of hyperpolarized lactate, pyruvate, alanine, bicarbonate with a temporal resolution of 3s. This approach could contribute to improving understanding of the role, in vivo, of lactate dehydrogenase, pyruvate dehydrogenase, alanine aminotransferase and monocarboxylate transporters, as well as the neuroprotective role of lactate in ischemic stroke.

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PROBING RENAL PH USING HYPERPOLARIZED [1-13C]ALANINAMIDE

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Hyperpolarized molecular probes can be effectively used as pH markers. To date, the only two probes reported \textit{in vivo} as extracellular pH sensors are \textsuperscript{13}C- bicarbonate [1], and [1,5-\textsuperscript{13}C\textsubscript{2}]zymonic acid [2],[3]. Alaninamide [4, 5] is a derivative of alanine which is found to be sensitive to variations of pH in the physiological range. The aim of the present study was to assess the feasibility of using alaninamide as a pH probe \textit{in vivo}.

The alaninamide titration curve was determined by performing \textsuperscript{13}C NMR measurements at 9.4 T, 37° on a set of 500 mM Ala-NH\textsubscript{2} HCl samples of varying pH referenced to \textsuperscript{13}C urea. [1-\textsuperscript{13}C]Alaninamide was polarized at 1 K in a 7 T polarizer, then rapidly dissolved in a buffered solution and injected IV into a Sprague Dawley rat (n=6) located in a 9.4 T animal scanner. \textsuperscript{13}C FIDs were acquired with 30° BIR4 pulses using a single loop \textsuperscript{1}H / quadrature \textsuperscript{13}C surface coil placed over the left kidney. The pH was perturbed by injecting acetazolamide IV (10 mg/kg) one hour prior to infusion.

The alaninamide titration curve shows a \textsuperscript{13}C\textsubscript{1} chemical shift change of \approx 8.4 ppm, and a pK\textsubscript{a} of 7.9. The pH sensitivity of \textsuperscript{13}C\textsubscript{1} results in three distinct alaninamide spectral peaks, corresponding to three different extracellular pH compartments within the kidney (pH = 7.46, pH = 7.22, pH = 6.58) that can be tentatively assigned to the cortex/blood, medulla and calyx/ureter. With acetazolamide treatment, the pH in the first compartment follows the change in pH of the blood, while the pH in the third compartment does not reflect the urine pH and shifts during the brief experiment. No change is observed in the pH value of the second compartment.

Hyperpolarized [1-13C]pyruvate MRS reveals increased aerobic glycolysis in the ultra-early phase of PSA-negative prostate carcinogenesis

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Hyperpolarized [1-13C]pyruvate magnetic resonance spectroscopic imaging (MRSI) is a promising technique that allows noninvasive assessment of pyruvate conversion to lactate, which is significantly higher in the solid tumors [1]. First-in-human study for metabolic imaging of prostate cancer is ongoing [2]. Very recently, we have reported the use of this approach for noninvasive assessment of therapeutic response to LDH inhibitor for mice-bearing tumor xenografts of PSA-negative human prostate carcinoma (DU145, PC-3) [3]. In the present study, hyperpolarized [1-13C]pyruvate MRS was employed to detect metabolic alterations in the early phase of three-dimensional (3D) organization of these cells. The cells were grown by the static culture using a spheroidal dish (EZSPHERE, i.d. 400~500 μm; 100~200 μm in depth/well, AGC TECHNO GLASS) for 6-10 days. Each prostate carcinoma cells (DU145: ~10 μm, PC-3: 20-30 μm i.d.) organized 3D cell spheroids of approximately 10-fold in diameter (DU145: ~100 μm, PC-3: ~250 μm on average). In these cell spheroids, the lactate/pyruvate ratio significantly increased (DU145: 9.8-fold, PC-3: 9.2-fold) as compared with those of monolayered culture, correlating to the ones from in vivo measurement [3]. Gene expression involved in the pyruvate metabolism as well as anti-tumor drug resistance increased as well, indicating that such tissue-like 3D cell proliferation, even in the tiny spheroids, induced the increased aerobic glycolysis. Thus, HP[1-13C]pyruvate MRS can be a biomarker for detecting PSA-negative carcinogenesis in the ultra-early phase, if much higher performance of HP measurement is realized.

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Aspartic acid is involved in several central metabolic pathways, including gluconeogenesis, the urea cycle, de novo nucleotide synthesis, the malate-aspartate shuttle, and via transamination the TCA cycle. The conversion in vivo of hyperpolarized [1-\(^{13}\)C]pyruvate to aspartate, via pyruvate carboxylation to oxaloacetate, has been reported in rat kidney [1] and in the mouse liver [2]. Additionally, the metabolism of hyperpolarized [1-\(^{13}\)C]aspartate to oxaloacetate has been noted in cultured cells supplemented with 2-oxoglutarate [3]. Aspartate is also of interest with its conversion to succinate in ischemic tissue implicated in subsequent reperfusion injury [4]. Here we report initial experiments with hyperpolarized [1-\(^{13}\)C]aspartate in the rat kidney.

[\(^{13}\)C]Aspartic acid was formulated with OX063 trityl radical as in [3] as the tris salt, with the addition of glycerol (14% v/v) to improve glassing. The formulation is highly viscous and dissolves poorly, limiting the usable dose. Experiments were performed in a 9.4T animal scanner and a 7T polarizer operating at 1K, with automated rapid transfer and infusion. Rats (n=2) were isoflurane anesthetized, a femoral vein catheterized, and a quadrature \(^{13}\)C surface coil placed over the kidney. Respiration-triggered (TR ~3s) pulse-acquire (BIR4-30\(^\circ\)) scans were started at the time of infusion of [1-\(^{13}\)C]aspartate (~16 \(\mu\)mol/kg in 1.2 ml).

Three metabolites were detected, with chemical shifts of 183.51 ppm (1.5%), 182.31 ppm (0.5%) and 181.26 ppm (0.6%), corresponding to [1-\(^{13}\)C]malate, [4-\(^{13}\)C]malate and an unidentified species provisionally assigned as N-acetyl[1-\(^{13}\)C]aspartate. [4-\(^{13}\)C]aspartate was at natural abundance, but [4-\(^{13}\)C]malate results from conversion to fumarate or succinate and label scrambling, and the greater prominence of [1-\(^{13}\)C]malate indicates oxaloacetate as an intermediate. These results show the potential of hyperpolarized [1-\(^{13}\)C]aspartate as an in vivo metabolic probe.

EXPLORING THE POTENTIAL OF HYPERPOLARIZED $^6$Li TO STUDY LITHIUM BIO-DISTRIBUTION IN THE RAT BRAIN

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Dissolution DNP can be successfully applied to hyperpolarize $^6$Li$^+$ salts to high levels [1,2]. As lithium salts are widely used for treating bipolar disorder, the aim of the present study was to evaluate the potential of hyperpolarized lithium-6 as a theranostic agent and to study its bio-distribution in the rat brain at pharmacological concentrations. In vivo measurements were carried out in a 9.4T animal scanner. A dedicated coil was designed and consisted of a modified Alderman-Grant coil tuned to $^6$Li and a $^1$H surface coil. HP $^6$Li solution was prepared by freezing droplets of glycerol:H$_2$O (1:1, v/v) containing 3M $^6$LiCl and 58mM TEMPOL radical. Samples were dynamically polarized using a custom-designed DNP polarizer operating at 7T (197GHz/1.00±0.05K) [3]. Sodium ascorbate was added to scavenge the radical prior to sample transfer [4]. The sample was dissolved and transferred into a separator/infusion pump located inside the magnet bore. 1.2mL of HP $^6$Li$^+$ solution was automatically infused into the femoral vein of male Sprague-Dawley rats [5], resulting in a $^6$Li$^+$ blood concentration within the therapeutic window (0.98mM). Data acquisition was triggered at the time of injection and a series of $^6$Li 1D spectra were acquired using 30° hard pulses every 5s. In order to evaluate the blood and tissue compartments of the detected $^6$Li signals, we repeated the same measurements but this time injecting Gd$^{3+}$-contrast agent 100±5s after the infusion of HP $^6$Li$^+$ (Gadovist 1M/1mL). To estimate the influence of hemodynamic on the acquired signal, another set of measurements were carried out, in which a 90° saturation pulse is followed by 30° pulses every 5s. We demonstrate that hyperpolarized $^6$Li can be detected at pharmacological concentration in the rat head with high SNR (Fig.1A). Upon injection of Gadovist the $^6$Li signal decays rapidly, indicating that $^6$Li$^+$ is mostly located in the vascular system and that its uptake in the rat brain during the length of our measurements is low (Fig.1B). The signal profile after a 90° pulse reflects the cerebral blood inflow (Fig.1C).

Analysis of dDNP NMR metabolic data from cancer cells

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With the rise of the field of systems biology, metabolomic data have been integrated with the data for other -omic sciences, and these gigantic collections of correlated data have with the ever improving computing power, been data mined to locate biomarkers and motifs.[1]

In this project the metabolic fingerprint of four prostate cancer cell lines, with different levels of aggression were analyzed. Metabolic data were obtained by incubating the cells with $^{13}$C$_6$-d$_7$ isotope labeled glucose, then quenching the metabolism, removing the cell debris and hyperpolarizing the metabolite extracts with dissolution Dynamic Nuclear Polarization (dDNP).

By integrating the peaks of the resulting NMR spectra, a collection of metabolic data was obtained without the need for identification of specific compounds. On this data, data mining was applied, with the aim to identify biomarkers of cancer and to classify the aggressiveness of the cancer.

The illustrations below show examples of obtained NMR spectra for the different cell types (on the left) and Principal Components-Discriminant Function Analysis (PC-DFA) results from the four prostate cancer cell types and a breast cancer cell line, in red, (on the right). The PC-DFA is clearly able to separate the cell types, with the most aggressive clustering together (blue and green).

As dDNP MNR have been shown to be quantitative and reproducible,[2] it could be an important tool in the future for cancer diagnostics.

Assessing \( \gamma \)-glutamyl transpeptidase activity in kidney using hyperpolarized \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly

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Hyperpolarized \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly provides a non-invasive means to detect \( \gamma \)-glutamyl transpeptidase (GGT) enzyme activity in vivo with potential for application in functional imaging. Since GGT is most abundant in the proximal tubules of the kidney [1], and since the properties of \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly are suitable for in vivo hyperpolarized \( ^{13} \)C metabolic analysis, it was proposed as a molecular probe to study kidney function [2]. The aim of the present study is to identify the dose of \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly that gives high NMR sensitivity in the unsaturated state of the GGT enzyme.

Therefore \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly was polarized with the stable trityl radical OX63 in a custom-designed DNP polarizer (7T, 1.1K) using microwave irradiation at 196.59 GHz and 50 mW. As a first approach to analyze the HP data, method used in [3] was applied. Herein, the reaction rates were calculated by multiplying the kinetic rate constants with the corresponding substrate concentrations, in which the kinetic rate constant is the product of the \( ^{13} \)C longitudinal relaxation rate of glycine (\( \sim 45 \)s) and the ratio of the integrated \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly and [1-\( ^{13} \)C]Gly signal amplitude.

Benefiting from a narrow spectral linewidth of the hyperpolarized signal (\( \sim 20 \) Hz, FWHM), conversion of \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly to [1-\( ^{13} \)C]Gly was measurable down to an estimated blood concentration of 32 \( \mu \)M. To address the possibility of substrate saturation of the GGT enzyme in the kidney, different doses of \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly were administered, corresponding to a blood concentration range of 32 to 500 \( \mu \)M. The variability of the apparent reactions rates between animals is high for all doses of administered \( \gamma \)-Glu-[1-\( ^{13} \)C]Gly. The rate, however, was proportional with the dose in 7 of 8 rats, and complete saturation of the GGT enzyme cannot be seen in the dosage range tested.

This study shows that HP \( \gamma \)-GluGly senses GGT activity with excellent NMR sensitivity and that a broad range of substrate concentrations can be applied to study kidney function. To understand better the distribution of the initial reaction rates and to estimate the dose required to saturate the GGT enzyme, a broader range of substrate doses will be tested, along with simultaneous functional quantification.

Hyperpolarized $^{13}$C MRI of the Human Brain


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There remains an unmet clinical need for improved imaging techniques that provide relevant characterization of cancer presence and response to therapy. An emerging approach for metabolic imaging using magnetic resonance is dissolution DNP [1] with $^{13}$C enriched substrates, with clinical studies currently underway at multiple research sites. In this work, we apply an imaging based approach to obtain initial data in healthy volunteers and patients with brain tumors, with the eventual goal of characterizing normal brain metabolism and response to therapy.

$[1-^{13}$C]pyruvate was prepared by a pharmacist and polarized using a 5T clinical polarizer (Spinlab, GE Healthcare). Pyruvate and radical concentrations, pH, polarization and temperature were measured prior to injection. A 0.43mL/kg dose of 246mM pyruvate (40% polarization) was injected at a rate of 5mL/s. The scan started 5s after the end of injection and 59s after the sample was dissolved. Imaging was performed on a 3T MR scanner using a $^{13}$C birdcage coil for RF excitation and a 32-channel coil for reception. Data were acquired with a metabolite-specific imaging sequence using a single-shot symmetric echoplanar trajectory [2]. A singleband spectral-spatial RF pulse was used to selectively excite pyruvate, lactate, or bicarbonate. Volumetric data were acquired with a 3s temporal resolution and a spatial resolution of $1 \times 1 \times 2cm^3$ for pyruvate and lactate and $2 \times 2 \times 2cm^3$ for bicarbonate using a multi-resolution approach [3].

**Figure 1.** Total signal (sum through time) showing pyruvate uptake and conversion to lactate and bicarbonate. Lactate was observed throughout the brain and subcutaneous tissues. Conversion to bicarbonate demonstrated a different spatial distribution, with highest signal in gray matter and lower relative intensities in white matter and subcutaneous tissues.

Puruvate uptake and metabolism through two enzymatic pathways was observed within a single injection (Fig. 1). Quantitatively, the peak dynamic SNR for pyruvate, lactate, and bicarbonate was 664, 159, and 142, respectively, in this particular exam. Ongoing studies in healthy volunteers will refine this approach using improved coil combination strategies [4] to characterize normal brain metabolism and determine the highest achievable spatial resolution, with the goal of acquiring dynamic $^{13}$C images in brain tumor patients at sub-centimeter spatial resolution.

HYPERPOLARIZED $^{133}$Cs IONS FOR INVESTIGATING MEMBRANE IMPAIRMENT IN CELLS

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$^{133}$Cs is an NMR active quadrupolar (spin 7/2) nucleus with 100 % natural abundance. The quadrupole moment is small leading to slow relaxation and narrow line widths in solution. $^{133}$Cs ions in a glassy matrix can be hyperpolarized employing trityl radicals. The polarization build-up at 3.35 T follows a bi-exponential path with a fast component resulting in 30 % solid state polarization in 5 minutes, and an end polarization exceeding 50 % (Figure 1 left, sample doped with gadolinium complex). A large part of the polarization is lost upon dissolution of the sample by an unknown mechanism but liquid state polarizations (10 s transfer time) of 15 % can be regularly obtained. The strong NMR signal enhancement thus obtained has made it possible to employ hyperpolarized $^{133}$Cs ions in biological experiments to monitor, with time resolution of seconds, the access of the ions to the intra-cellular environment of membrane impaired cells in suspension [1]. This is possible since the chemical shift of $^{133}$Cs is strongly sensitive to the chemical environment (e.g. the pH, ion strength and macromolecular crowding) [2] yielding a shift separation between intra- and extracellular fractions (Figure 1, right).

Figure 1. Left, typical $^{133}$Cs hyperpolarization build-up curve. Right, discrimination between intra- and extra-cellular fractions of hyperpolarized $^{133}$Cs ions

Interaction studies with secondary-labelled hyperpolarized ligands

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Hyperpolarization by dissolution-DNP\textsuperscript{1} provides a way of enhancing $^{13}$C MR sensitivity by more than four orders of magnitude on a wide range of small molecules. d-DNP can potentially be a game changer in numerous applications involving the observation of small molecule, such as metabolic imaging\textsuperscript{2}, metabolomics, drug discovery, or more generally analytical chemistry where NMR is often a method of choice to determine properties, structures and behaviors. However, to be truly useful in these applications, d-DNP would sometime require higher efficiency, throughput, and repeatability.

In this context, we have recently shown that by combining d-DNP with low temperature microwave-gated cross-polarization, unprecedentedly high levels of polarization could be attained in short times (60\% in 8 min)\textsuperscript{3}. We have also shown that a high level of repeatability could be afforded with our current d-DNP setup (CV=3.6\%)\textsuperscript{4}.

The main problem that remains when all these issues have been tackled is the fact that d-DNP generally relies on $^{13}$C spins which are of only 1.1\% natural abundance, and that most NMR applications such as metabolomics studies on natural products or biological samples are difficult to label. In 2009, Wilson et al. have proposed an approach where amine groups in amino acids where labeled with [1,1-$^{13}$C] acetic anhydride\textsuperscript{5}, and subsequently hyperpolarized, but this approach has not been taken up by the d-DNP community since.

Here, we propose to revisit this secondary labeling approach with our recent d-DNP advances and in the context of NMR fragment based drug discovery (FBDD). $^1$H ligand-observed approaches (STD / WaterLOGSY) is powerful for big protein (> 30 KDa) but can’t be applied for small proteins. We show how ligands can be secondary labeled and hyperpolarized to probe interactions with their target proteins (66 kDa and 8 KDa). We show that the labelling is used for an ultra-rapid interaction determination, via the detection of a change in hyperpolarized T\textsubscript{1} of the weak ligands $^{13}$C-tag. We are currently developing this new concept with the aim of decreasing by orders of magnitudes either the time or the concentrations required to detect ligands binding compare to classical approach.

pH-Dependency of the Spin-Lattice Relaxation Constant ($T_1$) of $^{13}$C-Labelled Hyperpolarized Biomolecules

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Hyperpolarized (HP) $^{13}$C-labelled biomolecules bear the potential to non-invasively characterize a variety of metabolic parameters such as enzymatic activity [1] or pH [2] using magnetic resonance spectroscopic imaging (MRSI). However, the major pitfall of HP-MRSI is the decay of the hyperpolarized state. This intrinsic process is characterized by the spin-lattice relaxation constant $T_1$. This molecule-specific parameter is influenced by a variety of environmental conditions such as magnetic field strength, temperature [3] or pH. Clinical HP systems filter out toxic radicals required for the polarization process at pH < 3, which might considerably influences $T_1$. In this work, the pH-dependency of $T_1$ was investigated for hyperpolarized [1-$^{13}$C]pyruvate and $^{13}$C-urea. 80 mM [1-$^{13}$C]pyruvate and 50 mM $^{13}$C-urea were hyperpolarized using a Hypersense polarizer (Oxford Instruments). The pH of the aqueous dissolution agent was adjusted using NaOH and HCl. Measurements were performed using a magnetic field strength $B_0 = 1$ T tabletop spectrometer (Magritek) applying a 5° RF-pulse every 5 s. Processing of spectra and fitting of signal decay curves was performed in MestReNova and Matlab. For pyruvate, $T_1$ is decreasing considerably under acidic conditions (-58% at pH = 2.5 compared to pH = 7, see Fig. 1a) due to increasing proton exchange close to the pK$_a$. Under basic conditions, this trend can be observed again, which is probably related to keto-enol-exchange processes. Analogous experiments were carried out for $^{13}$C-urea which has pK$_a$ far off the analyzed pH range. Thus, it most likely does not exchange protons with bulk water, which might explain why no significant pH-dependency on $T_1$ was observable (see Fig. 1b).

![Graphs showing pH-dependency of $T_1$ for hyperpolarized [1-$^{13}$C]pyruvate and $^{13}$C-urea.](image)

**Fig. 1:** pH-dependency of $T_1$ of hyperpolarized [1-$^{13}$C]pyruvate (a) and $^{13}$C-urea (b). Grey areas mark the pK$_a$ ± 0.5 of the molecule if applicable.

Our results suggest a strong pH-dependency of $T_1$ for molecules in pH regimes subject to proton exchanges or conformational changes. This is particularly interesting regarding pyruvate, since dissolution and transfer of hyperpolarized molecules can be optimized with respect to pH to finally improve the polarization level available for clinical experiments.

Dynamic Nuclear Polarization (DNP) is one of the most powerful hyperpolarization techniques used to overcome the low sensitivity of Nuclear Magnetic Resonance (NMR) experiments. Here we present a study of the DNP performance of BetaCyclodextrins enriched with $^{13}$C [1,2], a class of macromolecules which has important applications in Pharmacology and Nanomedicine, where only a few hyperpolarization studies have been performed. In order to achieve DNP the materials were doped with a variable concentration of TEMPO free radical. Proton DNP signal enhancement has been studied as function of TEMPO concentration and for a 1% of radical concentration in weight a maximum $^1$H polarization of 10% was obtained. $^1$H nuclear spin-lattice relaxation and polarization build up rates have been found to be consistent with the thermal mixing framework, the most efficient among all the DNP regimes [1]. However, since protons relaxation at room temperatures is too fast for possible future applications of DNP in these molecules, we have decided to enrich BetaCyclodextrins complexes with a variable amount of $^{13}$C nuclei. We observed that $^{13}$C DNP signal enhancement reached values up to 150, thus allowing a significant increase of the sensitivity of this nuclear species. It has been also observed that the more $^{13}$C nucliei are introduced, the better the DNP performance is, due to increase in nuclear spin diffusion. $^{13}$C nuclear polarization build up times are of the order of tens of seconds at 1.5-4.2 K, while $^{13}$C nuclear spin-lattice relaxation times at room temperatures are in the range 3-6 seconds [2], still too fast. In order to increase the spin-lattice relaxation time at room temperature we have studied the effect of deuteration on $^{13}$C hyperpolarization and spin-lattice relaxation. A significant increase in $T_1$ was detected, making our results a good starting point for the future application of DNP to BetaCyclodextrins for molecular imaging and high resolution NMR.

Generating Persistent Hyperpolarization with Porous Polarizing Polymers

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Hyperpolarization by dissolution dynamic nuclear polarization [1] has emerged in the last decade as a powerful tool for boosting the sensitivity of magnetic resonance imaging and spectroscopy by orders of magnitude. This has for instance brought metabolic imaging to reality [2]. Unfortunately, hyperpolarization’s lifetimes in all molecules hardly exceed a minute. This means that hyperpolarization needs to be produced ‘on-site’, which is for many reasons and in many cases unpractical. We have recently introduced a new concept for producing long-lasting transportable hyperpolarized molecules formulated in the form of micro-powders [3].

Here we will present the design and synthesis of new porous polarizing matrices based on straightforward and very versatile epoxy-based chemistry. We will show how the morphology of these materials (macro and meso porosity) can be tuned and how this affects the efficiency and lifetime of hyperpolarization. Finally, we will present DNP results obtained on the sole matrices, with absolute polarization values as high as P(1H) > 50% on the very first generation of these new materials. More interestingly, we have impregnated these polymers with solutions of [1-13C] urea and have been able i) to observe spontaneous 1H spin diffusion from the polymers to the frozen solutions and ii) to generate 13C hyperpolarization via cross-polarization that was persistent for more than 7 hours.

References :
Counterintuitive design of non-structured-HYbrid Polarizing Solids for Dynamic Nuclear Polarization

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Dissolution Dynamic Nuclear Polarization (d-DNP) has become a technique of choice for enhancing nuclear spin polarization as it offers a way to overcome the sensitivity limitations in NMR or MRI [1]. One of the most promising applications of d-DNP concerns metabolic imaging by MRI, where hyperpolarized solutions need to be pure and free of any polarizing agents (PAs). For this purpose, we have developed original-polarizing solids.

The last generation of solids, dubbed HYPSO 5 (HYPSOs standing for HYbrid Polarizing Solids) [2], was obtained by coating a uniform silica layer containing TEMPO radicals onto mesoporous silica spheres that exhibit a highly interconnected and unstructured 3D porous network. These materials allow to obtain contaminant-free hyperpolarized solutions and with optimized synthetic procedure, it was possible to finely-tune their physical and chemical features: 1) their texture (porous volume and pore-diameters) for a maximal impregnation of the solution of interest and for optimizing the spin diffusion process during DNP, 2) their particle size to ease their filtration and 3) their radicals concentration to reach higher polarization levels [3]. These new solids turned out to beat-up the previous generations of HYPSO solids, with a remarkable polarization efficiency of \( P(1^{1}H) = 71\% \) and \( P(1^{3}C) = 51\% \) for a sample containing 3 M \( [1^{13}C] \) sodium acetate in D_2O.

Microwave-Gated Dissolution Dynamic Nuclear Polarization


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Dynamic Nuclear Polarization (DNP) aims at transferring the large electron spin polarization to surrounding nuclear spins via microwave irradiation. Dissolution-DNP (d-DNP) experiments are usually performed in frozen samples doped with paramagnetic polarizing agents (PAs) where $^{13}$C polarization enhancements factors as high as 10'000 are possible with respect to thermal polarization in the liquid state [1]. We have recently implemented $^1$H→$^{13}$C cross-polarization (CP) during d-DNP experiment to further boost $^{13}$C enhancements to factors of about 50'000 [2].

However, $^1$H→$^{13}$C CP has so far been suboptimal because of the rapid proton relaxation in the rotating frame arising from the presence of PAs. We show in this work that $T_{1p}(^1H)$ can be significantly extended, and therefore CP greatly improved, by switching off the microwave irradiation briefly prior to CP. During this interruption, the electron spins relax from their partially saturated state to their highly polarized state ($P_e = 99.9\%$ at $B_0 = 6.7$ T and $T = 1.2$ K), so that paramagnetic relaxation becomes ineffective. As a result, $T_{1p}(^1H)$ is extended by several orders of magnitude and CP contact times can be extended to achieve optimum transfer.

The use of microwave gating in this context has two favourable effects; (i) preventing losses of proton magnetization during spin-locking and (ii) improving the CP transfer efficiency. Altogether, the efficiency of multiple contacts CP is greatly improved by microwave gating; polarizations as high as $P(^{13}$C) = 65$\%$ can be achieved in acetate with an overall polarization build-up time constant as short as $\tau_{bup} = 3$ min. A record polarization $P(^{13}$C) = 78$\%$ was even achieved in $^{13}$C labelled urea [3].

Boosting the dynamical nuclear polarization of [1-13C]butyrate with microwave frequency modulation

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\textbf{Introduction} - Hyperpolarization of [1-13C]butyrate via dynamic nuclear polarization (DNP) enables the measurement of short chain fatty acid (SCFA) metabolism in vivo [1,2]. The 13C label propagates into the tricarboxylic acid (TCA) cycle, making butyrate an interesting candidate for the quantification of mitochondrial metabolism, as both citrate and glutamate may be visualized [1,2]. Polarization levels of [1-13C]butyrate following DNP with conventional static microwave (MW) irradiation are reportedly on the order of 7-13\% [1,2,3]. Meanwhile, MW frequency modulation was shown to further increase maximum attainable polarization levels and shorten the buildup time [4] for radicals with wide electron spin resonance spectrum, such as TEMPO. This works aims at demonstrating that modulation can be applied for the enhancement of [1-13C]butyrate polarization.

\textbf{Methods} - All measurements were performed at 5T and 1.15K on a 5 M sodium [1-13C]butyrate sample dissolved in 2:1 (v/v) D2O:isobutanol and 50 mM TEMPO nitroxyl radicals. DNP of the sample was performed with and without frequency modulation by radiating 50 mW of 139.9 GHz microwaves. The frequency and amplitude of MW modulation was 10 kHz and 40 MHz, respectively. Additionally, thermal NMR signal was acquired for polarization quantification assuming Boltzmann polarization equilibrium.

\textbf{Results and discussion} - The use of MW frequency modulation reduced the buildup time constant by 55\% (from 6400 to 2880 s) and increased the maximum polarization by 58\%, resulting in a 12\% polarization level. The buildup time and maximum enhancement may be further improved using deuterated glycerol as glassing agent.

\textbf{Conclusions} – The use of MW modulation significantly improved the buildup time and maximum polarization of butyrate.

\textbf{References}
Metabolite profiles from cell extracts can be studied non-invasively in complex mixtures with NMR [1]. The advent of dissolution Dynamic Nuclear Polarization (dDNP) and isotope enrichment add sensitivity and resolution to such metabolic studies [2,3]. Metabolites can be mapped and quantified if protocols that control and exploit the ex situ signal enhancement are created. Here a reproducible and quantitative dDNP (qdDNP) NMR-based stable isotope-resolved analysis is demonstrated [4].

Living cells are incubated with uniformly $^{13}$C-labeled glucose at different time points, metabolites are extracted, hyperpolarized and subsequently analyzed with NMR allowing reconstruction of ex. cancer type specific metabolic pathways (Figure 1).

Robust quantification of metabolites demands that individual signal decay is taken into account. For all identified metabolites, a signal loss coefficient (SLC) was determined relative to the internal standard and compared to the ratio obtained with conventional thermal $^{13}$C NMR.

We demonstrate the use of this qdDNP assay for several cell types and discuss the possible advantages of using qdDNP in mixture analysis.

Low microwave attenuation and low thermal loss waveguides for dDNP probes

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Since the early demonstrations of dynamic nuclear polarization (DNP), microwave irradiation has been a requisite to transfer electron spin polarization to nuclear spins. Significant increase in NMR sensitivity by way of dissolution DNP (dDNP) [1] has encouraged the development of multiple commercial and home-built polarizing systems and consequently dDNP probes. The length of waveguide needed to couple a microwave source to the electron spins is dictated by the dimensions of the ‘polarizer’, thereby influencing the total waveguide attenuation. Additionally, the desire for higher magnetic fields ($B_0$) has raised the required microwave frequency to perform DNP, further limiting the available power due to inefficient solid-state microwave sources. Corrugated waveguides improve microwave irradiation by reducing transmission losses, but are costly to procure [2]. Similarly, mode converters offer use of propagation modes with reduced attenuation constants, but are challenging to fabricate at higher frequencies.

We herein present a solution to achieve efficient microwave irradiation as implemented for the dDNP probe in our most recent polarizer. The probe is permanently equipped with a waveguide coupling the top flange of the probe to the cryogenically cooled sample space, thus causing a ~290 K thermal gradient. To improve thermal isolation, a circular stainless steel waveguide ($\phi$4.16mm) is selected, since it offers the lowest attenuation to perimeter ratio, Fig 1. Ohmic losses are reduced by internally electroplating the waveguide with a 2-3 μm layer of copper. Waveguide attenuation was characterised for frequencies 94, 188 and 282 GHz, Fig 2. The attenuation of the lowest four modes in the copper plated waveguide is given in Fig 3, including HE$_{11}$ in an equivalent stainless steel waveguide with aluminium corrugation [2]. Fig 3 illustrates that the TE$_{11}$ fundamental mode is a good choice with little incentive to use corrugated waveguides or mode converters. In conclusion, less than 1 dB loss can be achieved across the frequency range 94-282 GHz with a low cost, simple to manufacture circular waveguide.

Versatile polarizer NMR spectrometer

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Hyperpolarization of nuclear spins using dissolution dynamic nuclear polarization (dDNP) lead to an increase of SNR in acquired NMR signals [1]. In vivo metabolic spectroscopy [2] and imaging [3] benefited from the boost in sensitivity leading to the development of commercial and home-built polarizer systems [4]. A basic spectrometer monitors the buildup of nuclear spin polarization prior to dissolution. These single purpose instruments are limited in SNR performance, bandwidth and transmitter frequency.

We herein propose an economical, dedicated polarizer spectrometer based on an integrated self-developed duplexer and the commercially available Magritek Kea2 NMR benchtop console (Fig.1). The spectrometer operates between 10 MHz - 450 MHz and offers two transmitting and one reception channels thus enabling the use of advanced pulse sequences. The duplexer’s T-R switch relies on PIN diodes and exchangeable λ/4 cables to provide a transmitter-LNA isolation less than +40 dB. An insertion loss less than 1.1 dB is observed during high power transmission (up to 300W using a Tomco TwinPulse 400 amplifier) and reception. High isolation and switching times 1-2 μs fulfil the hardware constraints needed for solid-state NMR. A Miteq AU-2A-150 LNA provides an average gain of 34.5 dB with a noise figure between 1.1 dB - 1.8 dB (Fig. 2).

The Kea2 and a Varian Direct Drive spectrometer were used to acquire 1H and 13C NMR signals for a 4.5 M [13C]urea (5:4:1 glycerol-d5, D2O, H2O & 40 mM TEMPOL) sample in a 6.7 T polarizer. The Kea2 spectrometer achieved an SNR of 483.1 and 84.2 with the Varian Direct Drive spectrometer obtaining an SNR of 1636 and 144.9 for 1H and 13C, respectively (Fig. 3).

HIGH PERFORMANCE FLUID-PATH FOR DISSOLUTION-DNP

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NMR’s intrinsic lack of sensitivity can be under some circumstances overcome with hyperpolarization by dissolution dynamic nuclear polarization (d-DNP) \cite{1}. One of the major challenges is the preservation of the hyperpolarization once the sample is melted as nuclear spin relaxation irreversibly drives it to Boltzmann’s equilibrium.

We have recently proposed the use of a magnetic tunnel \cite{2} to prevent excessive losses of polarization at low field during transfer. The group of Christian Hilty has extensively worked at speeding up this dissolution and transfer step by proposing an original design with fast valves that was further improved and later on equipped with high flow syringe pumps leading to flow rates up to 16mL/min and most recently even 150 mL/min \cite{3}, leading to total dissolution and transfer times as short as 1.6s.

Here we propose a design based on a micro gear pump (HNP Mikrosysteme mwr-11508X1) with flow rates exceeding 1100 mL/min. These pumps can drive hyperpolarized samples at pressure exceeding 3 MPa, resulting in measured transfer times as short as 0.6 s over 5-meter-long distances.

We will present the simple design of this new system (figure 1), including a fluid path featuring ultra-fast valves (8ms switching time) and a dedicated sample injector compatible with virtually any 5mm NMR probes. Finally, we will discuss on the performances of the system and the associated hyperpolarization results.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{d-DNP fluid path principally composed of a) a DNP sample holder at low temperature (T = 1.5K), b) a high speed switching valve (Valco AL10UW), c) a high flow pump (HNP Mikrosysteme mwr-11508X1), and d) a sample injector to collect the hyperpolarized solution at room temperature.
}
\end{figure}

\begin{thebibliography}{9}
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Refrigerated-bath cryostat for dissolution dynamic nuclear polarization

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Nowadays pulse-tube cryocoolers are replacing the venerable boiling-$^4$He cryostat [1] as the source of “cold” in laboratory-sized cryogenic experiments. A popular type offers up to 1.5 W cooling power at a temperature around 4 K. Such coolers can be used as a first stage in cryostats that must reach the typical temperatures for dissolution-DNP (1.0 to 1.5 K). The simplest scheme uses an additional closed He-loop, pumping on the sample bath with an external compressor that returns the pre-cooled fluid by flash evaporation through a needle valve into the actual sample bath [2]. In a DNP environment that bath temperature is typically 1.5 K.

A more elaborate scheme uses a static sample bath (closed, and not pumped) which is cooled through thermal contact with a separated $^4$He bath pumped on with a sorb pump during the working day and regenerated overnight [3]. Such systems can cool a DNP environment below 1 K.

We are developing a variant of the separated static sample bath scheme but instead of a sorb pump, the bath is cooled through thermal contact with a closed-cycle $^4$He refrigerator [4]. Such refrigerators have been developed as boosters for $^3$He/$^4$He dilution fridges. They can be fully push-button automatic without any user-adjustable component, and run 24/7 for months at a time [5].

For the moment our system is equipped with a nominally 100 m$^3$/h recirculating pump that provides 90 mW cooling power in the (empty) sample bath at 1.5 K, while the incorporated magnet is at 7 T field. Adding a DNP-insert system designed for a classical cryostat [6], we obtain a bath temperature of 1.40 K. For a [$^{1-13}$C] pyruvic acid sample doped with a suboptimal trityl radical concentration of 15 mM [7], we measured a solid-state $^{13}$C DNP-enhancement of 250, which corresponds to a polarization of 32%. We are working on improving the performances in our continuing development.

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Dynamic nuclear polarization (DNP) is a powerful technique to overcome the main shortcoming of regular NMR, which is its relatively low sensitivity. The essential idea is to take advantage of the high polarization of electron spins and transfer it to nuclear spins. To this end, samples are supplemented with a stable free radical often denoted as polarizing agent (PA). Nitroxide radicals like TEMPOL, which are extensively used in electron paramagnetic resonance (EPR) spectroscopy, are very popular for DNP applications as they can lead to remarkable proton polarization levels, frequently exceeding 80% at temperatures close to 1 K [1]. However, at the current stage, the origin of their performance is not entirely clear. To shed light on this, we performed pulsed EPR spectroscopy on prototypical DNP samples, i.e., hyperfine sub-level correlation (HYSCORE) and double electron-electron resonance (DEER) spectroscopy [2]. In the present work, typical DNP solvent mixtures consisting of 50% glycerol-d₈, 40% D₂O, 10% H₂O with varying concentrations of TEMPOL (1 to 50 mM) were investigated. The data unveil an unexpected inhomogeneous distribution of PAs as evidenced by intermolecular couplings between the unpaired electron of the PAs and the ¹⁴N nuclei of neighboring molecules (Fig. 1). The formation of dimers or multimers in solution, which are trapped through rapid vitrification near the glass transition temperature prior to use for DNP, may favor the cross effect (CE), which involves triple spin-flips of two electrons and one nucleus, thus explaining - at least in part - the good performance of TEMPOL in DNP of protons at temperatures close to 1 K.

Figure 1- HYSCORE spectra of a sample with 25 mM TEMPOL at B₀ = 3421 G with τ = 200 ns. The red arrows indicate evidence of intermolecular ¹⁴N hyperfine couplings.

Transferring frozen hyperpolarized droplets for dissolution DNP

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Dynamic nuclear polarization (DNP) is currently the subject of many new developments in view of boosting the sensitivity of NMR. Dissolution DNP is a promising approach, where samples are cooled to low temperatures (usually between 1.2 and 4 K), and where the high polarization of electron spins is transferred to nuclear spins by microwave irradiation. After rapidly dissolving the sample, the NMR spectrum is obtained at room temperature.

In the most widely used approach, the hyperpolarized frozen sample of ca 0.05 mL is dissolved with ca. 5 mL overheated D2O under ca. 1 MPa, and the resulting liquid is transferred through a ‘magnetic tunnel’ to the NMR instrument where the signal is acquired [1]. Inevitable losses of polarization due to relaxation can be reduced by increasing the speed of transportation. If the final solution is less diluted, the signal will be stronger. These are the main motivations behind the present work. The goal is to transfer hyperpolarized solid droplets pushed by pressurized gaseous helium as fast as possible to the NMR probe, where the dissolution will occur in ca. 0.5 mL of warm solvent, i.e., in a much smaller volume of solvent than is currently used. This is inspired by similar work by Meier et al. [2]. The design of our probe has been modified to accommodate a few small frozen droplets of ca. 0.01 mL each consisting of vitrified DNP juice that can be transferred to the NMR spectrometer for detection.

Sub-second dissolution-DNP at minimal dilution

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In dissolution-DNP, a sample containing hyperpolarized molecules such as pyruvate is dissolved with a jet of hot solvent propelled by helium gas. The solute is then transferred to a target magnet where strongly enhanced signals report structural and dynamic information, such as human metabolic fluxes in tumours [1,2].

D-DNP has great potential also in NMR spectroscopy, but substantial dilution and long transfer times often lead to disappointing results.

We are developing rapid-transfer dissolution-DNP, in which the sample is loaded into a bullet that is shot to the target magnet using pressurized helium gas, within typically 100 ms. A dissolution dock in the target magnet dissolves the sample (typically 50 uL) in 600 to 700 uL of aqueous solvent and reliably loads 5 mm NMR tubes within 700 to 800 ms. Polarization levels of several percent have been observed on 1-13C pyruvate, with a substantial potential for further improvements. We will present a detailed description of our implementation and compare the method to conventional dissolution-DNP.

APPLICATION OF BULLET-DNP TO PRODUCE LONG-LIVED HYPERPOLARIZED FUMARATE

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Hyperpolarized fumarate has been used in medical imaging to observe tumour activity in mice. [1,2] Perhaps the largest drawback to this form of imaging is the lifetime of the hyperpolarized NMR signals, which is often on the order of just tens of seconds.

We have recently shown it is possible to extend the lifetime of $^{13}$C nuclear spin polarization in fumarate molecules by temporarily precipitating them out of solution. [3] This is possible because at high field the solid state $T_1$ is significantly longer than the solution state $T_1$.

Using the new bullet-DNP technique, we demonstrate that hyperpolarized $^{13}$C nuclear magnetization of fumaric acid can be stored for times dramatically exceeding the solution-state $T_1$. A hyperpolarized bullet of fumaric acid in DMSO doped with trityl radical was fired into 12M HCl. The fumaric acid immediately precipitated, purifying it from the toxic radicals. The solid-state signal decay was measured for 60 s with 5° flip-angle pulses. NaOH was then added to dissolve the fumarate and we continued to measure the solution-state signal decay (Fig. 1).

We have measured the $T_1$ at 2 T and liquid nitrogen temperatures to be around 2 h, which should allow for application of this technique in transport and storage of hyperpolarized samples.


Figure 1: The hyperpolarized $^{13}$C NMR signal decay for solid and solution-state fumarate at 11.7 T, measured with 5° flip-angle pulses. In pink is the experimentally measured $T_1$ at 2 T and liquid nitrogen temperature of the same molecule.
Towards quantum-rotor-induced polarization in CH$_4$@C$_{60}$, methane endofullerene complex

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Endofullerenes are supramolecular complexes in which a small (endohedral) atom/molecule is confined within a bigger, fullerene, molecule which acts as an enclosing cage. Endofullerenes offer an ideal particle in a box system to directly observe quantum mechanical effects and the advantage of studying gas phase molecules in the liquid and/or solid state under ambient conditions when in endohedral form.

In the past two decades the field of endofullerenes has experienced impressive growth, with quite a few different molecules being confined inside fullerenes through “molecular surgery” [1-3]. Up until very recently the biggest endohedral molecule fully closed inside a cage was H$_2$O, however the work of R. J. Whitby et al. has taken it a step further, managing to enclose methane inside a C$_{60}$ cage.

Here we present a study of CH$_4$@C$_{60}$ through various NMR techniques. The effect of the endohedral methane on the C$_{60}$ cage was studied by measuring the $^{13}$C T1 of the cage with and without methane inside it at magnetic fields of 9.4 T, 11.7 T, 14 T and 16.4 T.

Relaxation measurements of $^1$H and $^{13}$C of the endohedral molecule were done to see if the confinement has an effect compared to the free molecule in the gas phase. Temperature dependent $^1$H T1 measurements, between 295-315K, performed at 700MHz indicated spin rotation as being the dominant type of relaxation mechanism for endohedral methane.

We intent to execute solid state cryogenic NMR measurements to see the behavior of endohedral methane and the C$_{60}$ cage at low temperatures (comparing with empty cage C$_{60}$) and to hopefully observe the different nuclear spin isomers of enclosed CH$_4$.

Finally, we expect to observe a quantum rotor induced polarization phenomena of endohedral CH$_4$, effect seen for freely rotating methyl groups [4].

Spin Isomer Conversion in Water Endofullerene at Room Temperature


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Molecular endofullerenes consist of a small molecule such as H2, H2O or HF encapsulated in a cage of carbon atoms, such as C60. The molecule is trapped inside the cage but is free to rotate. The H2 and H2O molecules have two distinct spin isomers: ortho and para with total spins of 1H nuclei 1 and 0 respectively.

At room temperature the ortho-to-para ratio in H2O@C60 is 3:1, but at low temperatures the equilibrium changes to essentially pure para water. Samples of H216O@C60 and H217O@C60 solutions were thermalised at 4.2 K to induce conversion into the para isomer. Then the samples were rapidly transferred into a high-resolution NMR magnet and dissolved in room temperature solvent. The conversion of excess para water to ortho leads to slow increase of 1H signal for H216O@C60. In H217O@C60 the conversion gives rise to an antiphase pattern in the 1H spectrum which is attributed to quantum-rotor-induced polarization. We estimate time constants for the para-to-ortho conversion at room temperature as 30 ± 4 s for H216O@C60 and 16 ± 3 s for H217O@C60 [1].

Master-equation for spin-systems far from equilibrium

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The recent developments in Magnetic Resonance clearly indicate an increasing interest in hyperpolarization techniques. Dynamic Nuclear Polarization (DNP), quantum rotor induced polarization (QRIP) and para-hydrogen induced polarization (PHIP) allow for the study of previously inaccessible systems. Polarization levels greatly exceed thermal Zeeman polarization and the spin-systems are far from equilibrium. As a consequence relaxation processes will equilibrate the spin-system with its environment.

Within the NMR community relaxation phenomena are often described by semi-classical relaxation theories [1]. The drawback of the semi-classical approach is that it cannot account for finite temperatures of the environment. The spin-system would therefore relax towards a non-physical equilibrium state. To correct for this misbehaviour a class of thermalization techniques have been developed [2, 3].

Recently we were able to report para-to-ortho conversion of water at room temperatures by means of rapid dissolution-DNP for the first time [4]. Description of the relaxation dynamics by means of conventional thermalization procedures led to wrong results. In general conventional thermalization procedures are not well-suited for spin-systems far from equilibrium.

We now propose a new thermalization technique which faithfully describes relaxation dynamics of spin-states far from equilibrium and generates the correct thermal state. The intuition behind our approach is based on the stochastic wave function approach [5]. Theoretical considerations are complemented by SpinDynamica simulations of simple model systems.

HYPERPOLARISATION USING THE BRUTE FORCE APPROACH


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We have previously shown that the brute force approach to hyperpolarisation (i.e. exposure to very low temperature and high field), in conjunction with nanoparticle-mediated relaxation enhancement, can yield very high nuclear polarisation on a realistic timescale [1]. We have also shown that the brute force method can be coupled with a dissolution system to yield hyperpolarised molecules in solution, in a similar manner to dissolution-DNP [2]. We have now brought together two low-temperature systems and a high resolution NMR spectrometer in one laboratory so that we can combine developments in relaxation enhancement with optimisation and automation of the sample ejection, dissolution, nanoparticle filtration and subsequent analysis. We will describe these systems for improved automation and reliability, as well as results and remaining challenges for improved enhancement in 1-13C pyruvic acid, both with and without Pt nanoparticles as ultra-low T relaxation agents. In this way we aim to bring the brute force method a step further towards providing a viable alternative and complement to dissolution-DNP and other hyperpolarisation technologies.

Many-body Kinetics of Dynamic Nuclear Polarization by the Cross Effect

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Dynamic Nuclear Polarisation (DNP) provides significant signal enhancement compared to conventional thermal polarisation techniques used in typical nuclear magnetic resonance applications. Of the possible DNP mechanisms, the cross effect (CE), involving triple spin-flips between two interacting electrons and a nucleus, is most efficient at low temperatures and microwave irradiation amplitude. In silico optimisation of parameters affecting CE enhancement, such as radical concentration or biradical design, require simulation of large spin systems. However, the computational expense of solving the Liouville-von Neumann equation for such systems makes this approach intractable after only a few spins. Here we show that the non-equilibrium nuclear polarization build-up is effectively driven by three spin incoherent Markovian dissipative processes. These processes can be modelled using a classical kinetic Monte Carlo simulation algorithm, giving us favourable scaling of simulation time with system size. With our theoretical approach, we have been able to simulate a system of over 100 spins, allowing for the first time the study of many-body processes such as spin diffusion.

Electron spectral diffusion and DNP – simulations and experiments

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It has been demonstrated during the last few years that the MW irradiation in static DNP at low temperatures results in a broad polarization loss over the EPR spectrum due to significant spectral diffusion [1]. It has been also shown that these steady-state electron polarization profiles determine the enhancement of nuclear polarization. In a recent publication we introduced a model 11 spin system combined with spin density matrix calculations to obtain insight into the spectral diffusion process [2]. In this study we will use this model system to calculate the result of electron double resonance (ELDOR) and DNP experiments. A comparison of these calculations to experimental results will demonstrate the role of cross relaxation in spectral diffusion. These calculations can also be extended to include the effects of the Solid Effect on the ELDOR spectra as well as reproduce experimentally obtained DNP spectra that are derived using the indirect Cross Effect [3].

PROTON HYPERPOLARIZATION FOR POLARIZED NEUTRON SCATTERING

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Scattering length neutrons for protons remarkably depends on relative direction of their spins. Thus, scattering pattern of polarized neutrons varies as a function of proton-polarization ($P_H$) of samples. Spin-contrast-variation (SCV) is a technique to determine structure of each component of composite materials from the $P_H$-dependent multiple scatterings (Fig. 1). The SCV has an advantage over conventional deuterium-labeled neutron scattering in the point that the same structural information can be obtained unless the deuterated model samples are prepared. Therefore, the SCV attracts potential users who have abandoned the neutron measurements due to difficulty of the deuterium labelling.

Since Knop et al. firstly demonstrated in 1989 [1], the SCV technique has been applied to small-angle neutron scattering (SANS) measurements. We have also carried out SCV-SANS measurements of variety of samples in Japan Research Reactor (JRR-3) and Japan Proton Accelerator Research Complex (J-PARC) [2-4]. Recently, we newly applied the SCV technique to neutron reflectometry to study surface and interface structure of multi-layered thin-films (Fig. 2) [5]. Now, we are developing SCV neutron powder diffractometry to determine polycrystalline structure.

Whereas the DNP apparatus in 1980’s was too large and tough to operate in neutron facilities, we make our system compact and improve its usability using modern techniques such as cryogen-free magnet and cryostat [5]. Our goal is to establish the SCV as a versatile technique of structure determination.


Fig. 1 In SCV, structure of each component of composite materials is determined from $P_H$-dependent scatterings of polarized neutrons.

Fig. 2 SCV-neutron reflectivity of thin-film block-copolymer on a Si block.
AN EXPERIMENTAL ACCESS TO THE MICROWAVE SATURATION FACTOR AT 9.4 TESLA DNP IN LIQUID STATE

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Liquid state (Overhauser) Dynamic Nuclear Polarization (DNP) experiments have been performed at high magnetic fields (9.4 T) on aqueous solution of $^{14}$N-TEMPOL nitroxide radicals. To determine the saturation factor of the electron spin, the $^1$H paramagnetic shift as a function of the microwave power was measured as previously reported [1]. We could show that both the diamagnetic shielding and the paramagnetic shift depend on the $^{14}$N-TEMPOL radical concentration. Both contributions can independently be determined by measuring the NMR line shift as function of the applied microwave power, which allows a quantitative determination of the DNP saturation factor.

COMPACT DNP POLARIZER FOR MRI APPLICATIONS AT 1.5 T

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Overhauser dynamic nuclear polarization of protons in water is used for MRI contrast improvement by means of a continuous flow DNP polarizer. Different from other approaches in our setup the hyperpolarization is achieved continuously [1] by administration of a physiological buffer flowing through a resonator under continuous microwave excitation with flow rate up to 1.8 ml/min, which can be used for MRI angiography applications in small animals like mice. Proton signal enhancements of more than 20-fold were achieved in phantoms with help of the DNP polarizer equipped with a multimode microwave resonator placed inside the bore of a 1.5 Tesla clinical scanner. The hyperpolarized substrate at physiological temperature can be routed with the help of a pneumatic switch to a 0.15 mm inner diameter quartz capillary for injection into the target object [2]. This approach allows hyperpolarization of protons without the need of an additional magnet and avoids losses arising from the transfer of the hyperpolarized solution between magnets. The performance of the polarizer will be described and the local sensitivity and contrast enhancements demonstrated with blood-vessel phantoms and with first applications to mouse.

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High Enhancement and Large Volume Overhauser Liquid DNP at 14.1 T

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In the liquid state, DNP is achieved via Overhauser mechanisms, scalar and/or dipolar, which have a complex dependence on the experimental conditions. Improving the signal to noise ratio, or polarization enhancement, by DNP in liquids is more challenging with increasing magnetic field. In this presentation, we illustrate our recent instrumentation development progress by showing enhancements of 160 for $^{31}$P and 70 for $^{13}$C nuclei at room temperature in large sample volumes (100 μL) that were obtained using a 395 GHz gyrotron at 14.1 T ($^{1}$H 600 MHz), see Figure 1. We will discuss the different Overhauser mechanisms and the development toward $^{1}$H DNP at 600 MHz. Finally, we will present our most recent instrumentation upgrade, which includes an in-situ EPR system based on a 395 GHz Virginia Diodes microwave source, along with continuous-wave and pulsed EPR spectra obtained for TEMPO and BDPA radicals, see Figure 2. A microwave field of 0.8 Gauss/Watt$^{1/2}$ at the sample is demonstrated for our homebuilt liquid DNP large sample volume probe. This corresponds to a microwave field of 2.4 Gauss at 10 W with the gyrotron.

![Figure 1. $^{13}$C NMR-DNP as labeled.](image1)

![Figure 2. in-situ EPR as labeled.](image2)
DYNAMIC NUCLEAR POLARIZATION ENABLES NMR REACTION/PROCESS MONITORING IN THE FAST FLOW REGIME

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Nuclear Magnetic Resonance (NMR) spectroscopy is a versatile non-invasive, quantitative and qualitative analysis method, established in a wide range of applications in medicine, physics, chemistry, and biology. NMR spectroscopy suffers from sensitivity due to the intrinsic low polarization of spins at ambient temperatures. To overcome this lack of sensitivity many hyperpolarization techniques were developed in the last decades, e.g. Dynamic Nuclear Polarization (DNP). In the following a mobile setup for continuous Overhauser DNP-enhanced NMR reaction/process monitoring is presented.

NMR detection is performed with a mobile, medium-field NMR spectrometer (bench-top, 43.2 MHz) due to many advantages of the device, e.g. low weight (55 kg) and adequate shim settings. Continuous hyperpolarization by Overhauser DNP enables the NMR measurements in the fast flow regime of liquids at ambient temperatures. This is of enormous interest to get direct insight into the monitored reaction/process. The lifetime of the hyperpolarized state is increased by immobilizing the radical 4-amino-TEMPO on the organic support sepharose [1, 2] and separating the hyperpolarized fluid from the radical matrix after hyperpolarization. 1H-NMR spectra are recorded of water, acetonitrile and mixtures of both components at different flow rates from 0.25 g min⁻¹ to 1.00 g min⁻¹.

Fighting the lifetime issue of NMR hyperpolarisation

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Despite its wide applicability in natural sciences and medicine, Nuclear Magnetic Resonance (NMR) still suffers from its inherently low sensitivity. This problem, which affects in particular Magnetic Resonance Imaging (MRI), can be addressed by various hyperpolarisation techniques, such as Dynamic Nuclear Polarization (DNP), Parahydrogen Induced Polarisation (PHIP) and Laser Polarisation of noble gases. Exploiting the large signal enhancements associated with these techniques NMR or MRI qualify for monitoring dynamic processes in real time. Via DNP and PHIP a large number of different molecules in the gas (PHIP), liquid (PHIP, DNP) and solid (DNP) phase can be hyperpolarised.

Each hyperpolarisation technique has found important applications, but several general problems remain. One severe limitation is the limited lifetime of the hyperpolarised state caused by $T_1$ relaxation. In liquids efficient relaxation processes restrict the hyperpolarisation to last from typically seconds to at best a few minutes. This drawback can be partially overcome by storing the fast decaying hyperpolarisation in long-lived spin states [1]. Another shortcoming inherent to all hyperpolarisation techniques is the partial destruction of hyperpolarisation by the application of RF-pulses which renders the usage of complex pulse sequences for multi-dimensional NMR experiments difficult.

An adequate concept to avoid these severe limitations is to use hyperpolarisation techniques in a continuous flow mode providing a continuous supply of hyperpolarized molecules. In this contribution the production of hyperpolarised liquids in a continuous flow mode using three different hyperpolarisation methods (PHIP, SABRE and Overhauser DNP) will be demonstrated [2, 3]. Moreover, it will be shown that PHIP is particularly well suited for the generation of hyperpolarized long-lived states in symmetrical molecules [4, 5].

SCALAR $^{13}$C-OVERHAUSER DNP IN THE LIQUID STATE AT LOW AND HIGH MAGNETIC FIELDS

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DNP in liquids is driven by electron-nuclear cross-relaxation, known as Overhauser effect (O-DNP). In the past, enhancements of $< 10^2$ were observed at room temperature at high magnetic fields ($> 1$ T) on $^1$H nuclei [1], due to the strong field dependence of dipolar relaxation. However, we recently reported $^{13}$C O-DNP enhancements at 3.4 T of three orders of magnitude [2], which were dominated by scalar hyperfine relaxation.

Here, we present an extension of this study to different magnetic fields on two model systems, i.e. CCl$_4$ and CHCl$_3$, doped with nitroxide radical (TEMPONE) as polarizing agent. Accurate determination of Overhauser parameters allowed us to disclose the primary role of the scalar hyperfine interaction to the $^{13}$C nuclei as mediated by either chlorine atoms or protons.

Experimental measurements performed at 1.2, 9, and 14 Tesla allowed us to complete the characterization of the polarization transfer efficiency, represented by the coupling factor, over a broad frequency range. Such field dependence can be successfully described by the subtle combination of dipolar and scalar relaxation.

Furthermore, a proper choice of polarizer can also be the key to optimize the efficiency of scalar O-DNP. Indeed, fullerene-nitroxide derivatives [3] are superior to TEMPONE radical at low fields, displaying at 1.2 Tesla a positive enhancement of ~800 in $^{13}$CCl$_4$, about 1.5 times larger than the one obtained with TEMPONE. Our results show the potential of O-DNP as a tool to address $^{13}$C-NMR sensitivity issues at different fields.


Singlet NMR has potential as a diagnostic tool, furthermore the combination of nuclear hyperpolarization and singlet NMR offers opportunities to develop novel MR imaging techniques. The design of molecules that allow access to the singlet state whilst attenuating the rate of relaxation occurring through different mechanisms is therefore critical to progressing research in this field.

Key criteria in the design of molecular systems that support long-lived singlet states include incorporation of a strongly coupled spin-1/2 pair; absence of spin-active nuclei in close proximity (through bond and through space) to the spin pair; nuclei such as $^2$H should also be as remote from the spin pair as possible; the local environment of the spin pair should exhibit inversion symmetry and a small chemical shift difference between the members of the spin pair is required.

Additional challenges posed for the synthesis of such molecules lies in the availability (and cost) of isotopically labeled starting materials and the incorporation of label at a specific site. There is also the need for unlabeled trial syntheses and a requirement for a specific final amount of compound to facilitate NMR studies. Furthermore, the final molecules should be stable and soluble under the desired NMR experimental conditions.

Based upon these design criteria, we present a range of organic molecules possessing a central $^{13}$C or $^{15}$N spin pair we have successfully prepared and tested for long-lived singlet lifetimes. An example, the octa-alkoxy substituted isotopically labeled naphthalene derivative, is shown below [1].

Field-Cycling Long-Lived-State NMR of $^{15}\text{N}_2$ Spin Pairs

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The applications of nuclear magnetic resonance spectroscopy and imaging are limited by the short lifetimes of conventional magnetization in solution. Systems containing homonuclear spin-1/2 pairs are immune to in pair dipole-dipole relaxation, with other symmetric decay mechanisms strongly attenuated. Long-lived states therefore provide an opportunity to alleviate this limitation.

A number of molecular structures exhibiting large ratios of the long-lived state lifetime $T_{LLS}$ to the spin-lattice relaxation time $T_1$ have previously been demonstrated. An asymmetric cis-fumarate diester supports a proton long-lived state of ~10 minutes and a $T_{LLS}/T_1$ ratio of ~50 at high field [1]. A ~77 minute long-lived state is provided by a $^{13}\text{C}$-labeled naphthalene derivative in room temperature solution [2], and a $^{15}\text{N}$ labeled diazirine spin pair exhibits a long-lived state of ~23 minutes at low field [3]. The long-lived state of $^{15}\text{N}$-nitrous oxide has been recorded utilizing field-cycling equipment and surpasses 26 minutes in solution [4].

We present an experimental case of a long-lived state for a $^{15}\text{N}$ labeled molecular system in solution. We observe a strongly biexponential decay for the long-lived state, with the lifetime of the slowly relaxing component exceeding 40 minutes. A relatively large relaxation time ratio $T_{LLS}/T_1 \approx 21$ is observed. Although the spin-lattice and long-lived state relaxation times are relatively short at high field, impressive relaxation times are unveiled at low field. Experiments at low field make use of a dedicated two-field NMR spectrometer with sample shuttling capabilities. The decay characteristics of the long-lived state are examined, and provide evidence for scalar relaxation of the second kind, induced by nearby deuterium nuclei.

These results are encouraging for the future construction of core molecular units which may support long-lived states, and demonstrate that $^{15}\text{N}_2$ systems house a suitable target spin pair. We are currently investigating other molecular candidates of this kind. We anticipate that similar spin systems may be easily hyperpolarized, or functionalized for various applications.

Long-lived nuclear singlet states (LLS) possess lifetimes significantly longer than typical relaxation times in NMR and have immediately evident potential for the storage and transport of hyperpolarized nuclear spin order. The utility of a particular LLS is determined by its singlet relaxation lifetime $T_S$ which is limited by various factors, such as the dipole-dipole (DD), chemical shift anisotropy (CSA), and singlet-triplet leakage (STL) interactions. The theory and equations modeling these interactions are well-described in the literature. In practice, rather than design some "ideal" LLS molecule to be synthesized, it is synthetic feasibility which dictates what molecules are LLS candidates – and the making of these molecules can be extremely expensive and difficult when asymmetric synthesis and isotopic enrichment with rare isotopes (e.g. $^{13}$C or $^{15}$N) is involved! There is thus great motivation to be able to guide syntheses by computationally modeling feasible molecules in silico and identifying the most ideal i.e. longest $T_S$ LLS candidates to be made. We use the Gaussian™ package to produce energy-minimized structures of LLS candidates at a suitable level of theory, integrating these geometries within a custom code in Mathematica™ to rapidly produce estimates of the upper limit of $T_S$ as governed by the field-independent DD interaction. We also show that - using the results of DFT-GIAO calculations on the same molecules – that it is possible to use calculated chemical shift tensors and J-coupling values to include the CSA and STL interactions, producing an estimate of $T_s$ as a function of magnetic field strength. This computational approach has immediate applicability in the pre-trialing of LLS candidates which are often expensive with time-consuming synthetic routes that have no guarantee of success.
Design of Long-lived Hyperpolarized Molecular Probes and Applications

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Hyperpolarization is a highly attractive technique in biomedical MRI or MRS applications as it enables sensitive detection of metabolic reaction of $^{13}$C/$^{15}$N-labeled molecular probes \textit{in vivo}.\textsuperscript{[1]} However, the hyperpolarized molecular probes often suffer from a critical problem, that is a short lifetime of hyperpolarized spin state. In typical $^{13}$C molecules, hyperpolarized spin state rapidly decays back to thermal state in an order of second. This problem has hampered a design of various hyperpolarized molecular probes and the number of hyperpolarized molecular probes, that work \textit{in vivo}, is still limited.

Based on this background, we have taken a challenge to produce a design strategy to develop hyperpolarized molecular probes,\textsuperscript{[2–7]} especially those that can retain hyperpolarized spin state for a long time. By minimizing the size of enzymatic substrates, hyperpolarized molecular probes for $\gamma$-glutamyl transferase\textsuperscript{[2]} and aminopeptidase\textsuperscript{[3]} were developed. In addition, we have proposed a "platform-type design strategy". By using core platform structures $^{13}$C-tertbutylbenzene\textsuperscript{[5]} and $^{15}$N-TMPA\textsuperscript{[6,7]} which have extremely long $T_1$ values of 141 s (9.4 T, CD$_3$OD, 25 °C) and 1177 s (9.4 T, D$_2$O, 30 °C), respectively, it was demonstrated that variety of hyperpolarized molecular probes could be designed.

Recently, we are trying \textit{in vivo} applications of these new hyperpolarized molecular probes. In this presentation, I will introduce recent advancements in the design of these hyperpolarized molecular probes and trials for \textit{in vivo} applications.

High-performance modular probe assemblies for microfluidic nuclear magnetic resonance spectroscopy

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Miniaturised NMR detectors have better mass-sensitivity compared to the conventional liquid-state NMR (Nuclear Magnetic Resonance) probes due to their higher filling factor. We present a transmission line based [1] novel modular design of an NMR probe assembly for high sensitivity generic microfluidic NMR experiments. The main advantages of this new probe design are its high sensitivity, high resolution, and modularity. The NMR detector including the tuning and matching circuit of the probe is modular. This allows the usage of a single probe base with many detectors optimised for different experimental conditions like mass sensitivity, concentration sensitivity, sample volume, single or dual channel etc. The sample is loaded in an exchangeable microfluidic device. NMR spectra with sensitivity around 1 nMol/sqrt(Hz) and a resolution of better than 0.01 ppm from 2 μl of fluid have been recorded. Generic 1D (A, DMEM cell growth medium) and 2D (B and C, 100 mM \textsuperscript{13}C glucose and 1 mM \textsuperscript{15}N ubiquitin respectively) NMR experiments have been successfully performed at different magnetic fields.

Comparison of the hyperpolarization of different fluorinated aromatic systems via photo-CIDNP

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Numerous aromatic molecules have important roles in human metabolism, e.g., tyrosine is a precursor for the neurotransmitters DOPA and a potential biomarker of gastroesophageal cancer.[1] To study the MR signal enhancement of such molecules we present a MR spectroscopic examination of the hyperpolarization of four fluorinated aromatic systems in aqueous solution by using the hyperpolarization technique photo-Chemical Induced Dynamic Nuclear Polarization (photo-CIDNP).[2,3]

A low cost LED set-up (Cree XP E high power LED (455 nm))[4,5] was used for irradiation inside a sample containing a 2 mM solution of 2-fluoro-tyrosine, 3-fluoro-tyrosine, 3-fluoro-4-hydroxybenzoic acid respectively 4-hydroxy-3-(trifluoromethyl)benzoic acid and 0.2 mM riboflavin 5’-monophosphate sodium salt hydrate and 600 µl physiologic salt solution, respectively D2O. NMR measurements on a 7T MR system (Bruker WB-300 Ultrasound) occurred by using 90° pulses (1H: P1 = 29 µs, PL1 = 15 W; 19F: P1 = 32.5 µs, PL1 = 17 W).

For example the 19F NMR spectra of 3-fluoro-4-hydroxybenzoic acid, measured after different irradiation times, are shown in Figure 1. A signal enhancement (SE) factor of up to 5 could be observed. In case of 3-fluoro-tyrosine an SE of >10 is detectable without heating the sample.

![Figure 1: 19F NMR spectra of 3-fluoro-4-hydroxybenzoic acid in D2O.](image)

HYPERPOLARIZATION-ENHANCED 2D NMR OBSERVATION OF PROTEIN FOLDING IN REAL-TIME

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Although mainly applied to the study of protein structure at equilbrium, NMR spectroscopy affords the opportunity to directly follow changes in the local environment of individual atoms 'in situ', i.e. as the native backbone fold is formed and the compact hydrophobic core of a protein is established. When applied in a one-dimensional fashion, however, these real-time NMR methods frequently suffer from low spectral resolution and the acquisition of kinetic spectra of higher dimensionality is often limited by relatively long acquisition times and/or lower sensitivity.

Here, we propose a side-chain-selective and highly sensitive way of conducting heteronuclear 2D NMR experiments repetitively to monitor protein folding processes in real-time. This is achieved by combining three key methodologies: i) rapid mixing of sample solutions to trigger protein refolding 'in situ'; ii) photo-CIDNP, a nuclear spin hyperpolarization phenomenon highlighting solvent-exposed tyrosine, tryptophan, and histidine side chain nuclei by means of a light-induced reaction of spin-correlated radical pairs; to this, we add here (iii) fast acquisition of heteronuclear 1H-15N HMQC photo-CIDNP data in real-time featuring a specifically tailored 2D NMR pulse scheme based on the SOFAST method. Employing the protein BLA, it is demonstrated how this approach can be used to productively combine the advantages associated with the photo-CIDNP technique as applied to amino acids and proteins, e.g. strong 1H and, in particular, heteronuclear signal enhancement of up to two orders of magnitude, rapid build-up of nuclear polarization, high amino acid side-chain selectivity and a concomitant simplification of protein spectra, with the benefits of 2D NMR spectroscopy – usually performed at equilibrium, e.g. spectral resolution enhancement which facilitates the observation of structurally disrupted protein states, straightforward detection of heteronuclei, and the ability to observe larger proteins as compared to one-dimensional NMR.

It is believed that these kinetic experiments can be used in the future as a complementary tool to existing one- and two-dimensional NMR analogues providing a side-chain selective, atomic-level insight into the structural transformations occurring during (multi-step) protein folding processes. Owing to the chemical signal amplification associated with the technique, these methods might prove particularly suitable for the identification and structural examination of lowly concentrated intermediate structures – occurring, for example, in a transient fashion as folding progresses – or ill-defined protein oligomers often populated to a relatively limited extent and thus difficult to trace using standard approaches.
Aureochrome is a blue light receptor containing flavin mononucleotide (FMN) in its LOV domain. In natural occurring aureochrome LOV, light illumination would lead to a photoexcited triplet state of the FMN cofactor which then quickly reacts with a nearby conserved cysteine to form a covalent adduct. [1] A cysteine-to-alanine mutant abolishes the adduct formation and elongates the lifetime of $^3$FMN. This instead can induce one electron transfer from a nearby tryptophan residue (11 Å edge to edge) and form a radical pair which generates photochemically induced dynamic nuclear polarization (photo-CIDNP) in solid and liquid state NMR [2,3].

We explored the generation of carbon photo-CIDNP in the LOV-C287S mutant of Phaeodactylum tricornutum aureochrome with a uniformly $^{13}$C-$^{15}$N-labelled sidechain of tryptophan. Signal enhancement was significant and selectively for the tryptophan side chain, electron donor of the radical pair. According to signal assignment and intensity comparison in the $^{13}$C NMR spectrum, we derived the electron spin density distribution on the indole ring.

Together with the photo-CIDNP effect, photo-degradation of FMN in the mutated aureochrome and the LOV1-C57S mutant of Chlamydomonas reinhardtii phototropin was observed. It was investigated whether additives could mitigate the photo-degradation and prolong the lifetime of the protein. For this, small amounts of the biological reductant, tris(2-carboxyethyl)phosphine (TCEP), were added to the protein solutions and investigated under one hour continuous blue-light illumination with UV/Vis spectroscopy and $^{31}$P-NMR. Recent results will be presented.

EXPLOITING RADICAL TRIPLET PAIR HYPERPOLARIZATION FOR SENSITIVITY ENHANCEMENT IN SOLUTION STATE NMR

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DNP-NMR methods tackle the low thermal polarization of nuclear spins by microwave-pumped polarization transfer from more strongly polarized electron spin systems, yet in most cases thermal electron spins are used. Significantly larger enhancements, exceeding the 660-fold ($\gamma_e/\gamma_H$) limit, are potentially possible using hyperpolarized electronic spin states, as are generated optically via the mechanisms of Spin Chemistry. The use of optically generated electronic hyperpolarization arising through a radical pair mechanism to provide selective NMR signal enhancements in photo-CIDNP is already well known [1]. Here we present our recent demonstration of an alternative method (Fig. 1), using electronic hyperpolarization arising through a radical-triplet pair mechanism (RTPM) to provide bulk sensitivity enhancements in solution-state NMR [2]. Whereas photo-CIDNP typically relies upon a spin-selective photochemical reaction of a triplet with specific amino acid residues (Tyr, Trp and His) the RTPM is a photophysical process that can hyperpolarize extrinsic persistent radicals. As in Overhauser DNP these radicals undergo cross-relaxation, transferring polarization to coupled nuclei with resultant NMR signal enhancements. DNP methods typically involve driving polarization transfer by microwave pumping of electronic transitions. Hyperpolarizing the electron spins by optical pumping could offer much larger enhancements, overcoming the Boltzmann limit, whilst also removing the need for the technically demanding microwave irradiation step as the hyperpolarized radicals undergo cross-relaxation without any further driving radiation.

Alongside our proof of principle demonstration of RTPM enhanced NMR [2] we report recent progress in optimizing the method, interpreted using the Overhauser equation. Combining numerical modelling of time-resolved EPR investigations with recent kinetic studies [3] has further developed understanding of the radical-triplet pair system. Correlating this data with NMR measurements we have identified the solution conditions that maximize the DNP enhancement, and have exceeded our previously reported enhancements despite no longer using deuterated solvents.

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Light-Induced hyperpolarization in reversible reactions of biomolecules

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We developed very efficient methods for creating light-induced spin hyperpolarization termed chemically induced dynamic nuclear polarization (CIDNP) [1] that can provide valuable data on the structure and reactivity of short lived radicals in biological systems at ambient conditions not obtainable by standard techniques.

The talk describes significant progress in three directions:
(I) development of hardware and new techniques for investigating hyperpolarization over a wide range of magnetic fields and microsecond time resolution at high field;
(II) development of theory and methodology of spin hyperpolarization in condensed media;
(III) application of spin hyperpolarization to the study of various chemical processes of biologically important molecules.

We continued with the development and application of methods of photo-induced nuclear spin hyperpolarization and relaxation in condensed media extending over a magnetic field range from 5 nT to 10 T. [2] According to our methodological developments, the studies are largely devoted to the application of spin-hyperpolarization methods to the study of reactions and processes involving short-lived radical species. New results were obtained on the study of fast radical reactions involving biologically important molecules, in particular on the structure and reactivity of such radicals. Photoreactions of various benzophenones with biomolecules were studied in detail focused on intra- and intermolecular electron transfer.

CIDNP of the pyrimidine bases of thymine and thymidine DNA was studied in detail. Results on formation and decay of a newly discovered unusual guanosine radical cation including its pH dependence will be presented. [3] An oxidation reaction with the DNA base thymine in the presence of photosensitizers produces other short-lived nucleotide radicals. Here the abovementioned advantages of the CIDNP method will be amplified.

The magnetic field dependence of CIDNP as a source of information about electronic exchange interaction will be shown for a number of promising molecular systems: in recently synthesized dyads, which can be used in photovoltaics, and in biradicals of the flavin-adenine dinucleotide molecule. [4] For signal enhancement methods based on field variation were developed to transfer polarization among protons and heteronuclei, as well as to create ”long-lived” polarization of hetero-nuclei as will be illustrated by various examples.

Nuclear Magnetic Resonance (NMR) and magnetic resonance imaging (MRI) play unique and critical roles in chemistry, biology, and clinical research where they impact directly on diagnosis. Both of these approaches would benefit from improved sensitivity and by using hyperpolarization via microwave driven dynamic nuclear polarization (DNP), the detected response can be improved by several order of magnitudes in liquid states. [1], [2]

Photo-induced radicals, generated by UV-light irradiation of frozen solutions containing a fraction of pyruvic acid, are suitable to perform DNP on several substrates. [3] The interesting property of such polarizing agents is their non-persistency as they recombine as diamagnetic compounds and can be quenched inside the polarizer when the DNP sample is still solid, providing the way for hyperpolarization storage and transport of hyperpolarized samples. [4]

Herein, we present the new and improved polarizing agents to overcome the actual limitation of low achievable $^{13}$C polarization, mainly associated with the broad ESR linewidth of radical generated from photolysis of pyruvic acid. The focus of the present study is on developing narrow ESR line radicals that results in unprecedented higher $^{13}$C polarization in liquid state.

UV-induced radical could be very interesting for $^1$H polarization as well since they can be destroyed before dissolution and loss of polarization due to presence of radical could be prevented. [5] Photo-induced radicals for $^1$H polarization have been explored with the focus on developing the broad ESR line radicals for efficient $^1$H polarization and to have no hazardous side products after radical quenching.

A narrow line UV-induced non-persistent radical to generate highly polarized transportable glucose solid samples


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Photo-induced radicals, generated via UV-light irradiation of frozen solutions containing a fraction of pyruvic acid (PA), are suitable to perform DNP on several substrates [1, 2]. The unique property of this polarizing agent is its non-persistency: they suffer from thermal stress and they are naturally scavenged if the temperature of the DNP sample is raised above 190 K. This feature has demonstrated a possible way to hyperpolarization storage and transport [3].

In the present work, for the first time, we use as radical precursor a pyruvic acid derivative that is not involved in metabolic pathways: trimethyl pyruvic acid (Tri-PA). Moreover its molecular structure provides a sharper ESR line compared to PA (see Fig A). The latter represents an advantage for DNP of $^{13}$C. The DNP properties of the new radical precursor were tested on glucose, a substrate showing increasing interest among the DNP community.

Tri-PA was added in concentration of 0.7 M to a solution containing 2 M of [U-$^{2}$H, $^{13}$C]glucose dissolved in a mixture H$_{2}$O:glycerol 1:1 (v/v). Frozen beads of the sample were UV-irradiated in liquid nitrogen for 300 s with a high power (20 W/cm$^{2}$) broad-band UV source (Dymax BlueWave 75) to generate a radical concentration around 40 mM. DNP was performed using a 6.7 T/1.1 K polarizer. Shining microwaves at optimal conditions (x mW at 188.19 GHz with 20 MHz/1kHz modulation), $^{13}$C was polarized up to 48±2 % in about 1 h (see Fig B). After dissolution and transfer (10 s delay) to a 9.4 T high resolution vertical NMR magnet a polarization of 29±1 % was measured (see Fig C). As comparison, an similar sample containing 30 mM Trityl instead of the UV-radical precursor, was prepared. In this case, 37±2 % $^{13}$C polarization was achieved in the solid state (20±1 % after dissolution). Using the same Trityl radical concentration we can routinely polarize [1-$^{13}$C]PA to 65 – 70 %. The results show that UV-irradiated Tri-PA combine efficient DNP properties to its natural thermal quenching above approx. 190 K, is a valuable and inexpensive polarizing agent for a challenging dDNP substrate such as glucose.

DNP of metal-organic frameworks using photo-excited triplet electrons

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DNP based on photo-excited triplet electrons (Triplet-DNP) has the potential to hyperpolarize nuclear spins of substrates in the low magnetic field at room temperature. In the typical scheme of DNP based on photo-excited triplet (Triplet-DNP), the spin-selective intersystem crossing (ISC) produces the large electron spin polarization in the excited triplet state sublevels. This polarization is effectively transferred to nuclear spins by pulsed microwave irradiation for satisfying the Hartmann-Hahn condition, so-called integrated solid effect (ISE, Figure b).

Conventional Triplet-DNP has been studied in crystalline or amorphous organic materials. The organic crystals have the long spin-lattice relaxation time (T1) of proton due to the rigid structure, which is advantageous for the effective accumulation of spin polarization. However, it remains difficult to accommodate other target molecules to be monitored. Amorphous solids allow the accommodation of target substrates, however, these flexible structures suffer from short T1. Therefore, it remains a challenge to develop a Triplet-DNP system that simultaneously concomitantly suppressed spin relaxation and accessibility for various polarizing targets.

In this work, we show the first example of employing metal-organic frameworks (MOFs) as host materials for Triplet-DNP. MOFs provides both rigid crystalline structures and nanopores for accommodating various target substrates, which feature has not been attained in the conventional Triplet-DNP systems. For the proof-of-concept, we employed a diamagnetic Zn (II)-based MOF, [Zn(MeIM-d3)2]n (D-ZIF-8), and introduced a polarizing agent PDBA (Figure a). Repeated polarization transfer from PDBA triplet electrons to 1H nuclei and subsequent spin diffusion in D-ZIF-8 with ISE sequence (Figure b) resulted in the large enhancement of 1H-NMR signals of D-ZIF-8 (Figure c).


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**Figure.** (a) Synthetic synthetic scheme for D-ZIF-8□PDBA. (b) Integrated solid effect (ISE) sequence for Triplet-DNP. (c) 1H-NMR signals of D-ZIF-8□PDBA under thermal condition (10scans every 3 minutes, black) and with Triplet-DNP (ISE sequence for 50 s and 1 scan, red) at room temperature.
The creation of hyperpolarized substrates via dissolution-DNP traditionally requires the sample to be doped with stable radicals that act as a source of polarization for the surrounding nuclei. It was shown that pyruvic acid-based non-persistent radicals can be photo-generated using UV light and hyperpolarize $^{13}$C-labeled metabolic substrates for dissolution DNP [1,2]. These radicals can subsequently be annihilated by bringing the temperature above 200K without affecting the $^{13}$C polarization, allowing the extraction and storage of hyperpolarized solids [3].

To date, most of the reported efforts were focused on the photo-generation of radicals on pyruvic acid. In the present work, we examined three different nitrite derivative compounds. Their suitability for dissolution DNP is explored through observation of the radical concentration and ESR line shape. The effect of the diluting solvent on the radical concentration and line shape will be presented. DNP is carried out to demonstrate the applicability of the created radical to the hyperpolarization process. The low boiling point (~40°C) displayed by these compounds means that the nitrite derivatives could be added to other substrates to be polarized and would be boiled off (and/or transformed in volatile alcohols) in the dissolution process leaving the substrate ready for in vivo experiments.

Molecules containing unpaired electrons (i.e. radicals) are an essential component for any sample to be hyperpolarised by Dynamic Nuclear Polarisation (DNP). Conventionally, these are supplied by doping the sample with persistent stable radicals such as trityl, TEMPO or BDPA [1]. However, these radicals accelerate polarisation decay after DNP and may be toxic. Therefore, they need to be removed from the hyperpolarised substance before it is used in clinical applications.

Photoinduced radical agents generated by ultraviolet (UV) irradiation are a promising source of unpaired electrons that can be annihilated after DNP (through thermalisation at around 200K) while preserving the high polarisation levels. This has been recently demonstrated in pyruvic acid [2,3].

Here we discuss photoinduced radicals derived from other oxoacids, which produce a high radical yield with narrow ESR linewidth. The photolysis of phenylglyoxylic acid produced up to 40 mM of radicals with a linewidth of 1.4 mT measured in an X-band ESR spectrometer. In this case, deuteration of the substrate led to a 10% narrower ESR linewidth. We have polarised DNP samples prepared with this type of photoinduced radicals in a custom-built 7T polariser. We will compare the performance of the methodology with existing clinical/preclinical practices and give an outlook for the future.

Room temperature hyperpolarization of equal mixtures of benzoic acid and other aromatic carboxylic acid

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Photo-excited triplet states of pentacene have suitable properties for DNP. Henstra et al. obtained a $^1$H spin polarization of 0.66% in a single crystal of naphthalene doped with pentacene even at room temperature using Integrated Solid Effect [1]. (Here, we call the method Triplet-DNP.) The enhancement factor was 5500, which is above theoretical limit for DNP using thermally polarized electron spins. We obtained a $^1$H spin polarization of 34% in a single crystal of partially deuterated $p$-terphenyl doped with deuterated pentacene [2]. Recently, we have also succeeded in dissolution DNP using benzoic acid doped with pentacene [3]. Although Triplet-DNP can be implemented in a low magnetic field and high temperature, it has an obstacle for NMR and MRI applications: pentacene can not be doped in a variety of molecules and, therefore molecules previously polarized by Triplet-DNP were limited. Here, we have demonstrated room temperature hyperpolarization of equal mixtures of deuterated benzoic acid and other aromatic carboxylic acid, which can not be highly polarized by Triplet-DNP without mixing of benzoic acid.

We deuterated benzoic acid to confirm a $^1$H signal originating from other aromatic carboxylic acid. We prepared benzoic acid-$d_6$ doped with 0.06mol% pentacene before mixing. We prepared three samples mixed the benzoic acid-$d_6$ and the molecule (salicylic acid, nicotinic or, 2-naphthoic acid) in a 1:1 mol ratio above the melting points. Hydroxyl protons in salicylic acid and nicotinic acid were deuterated to increase the $^1$H spin relaxation time. All experiments were carried out in 0.39T at room temperature. We obtained a $^1$H polarization of ca. 0.84% for salicylic acid (Fig. 1). All the points (circles) were acquired with the same sample by a 90° pulse. The pentacene in the sample was gradually degraded by the laser irradiation. Thus, to suppress the degradation, we carried out Triplet-DNP of another new freshly prepared sample for only 360s without measurement of the build-up of $^1$H polarization. Then we achieved a $^1$H polarization of 1.15% for salicylic acid as indicated by a triangle in Fig. 1. The $^1$H polarizations of nicotinic acid and 2-naphtoic acid were 0.36% and 0.33% without measurement of the build-up, respectively.

Transportable hydrogen solid state nuclear polarization

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In the methods of dynamic nuclear polarization (DNP), a high polarization of an electron spin system is transferred to the nuclei by means of a microwave field. These very electron spins are however also responsible for the decay of the nuclear polarization via spin lattice relaxation. Using short-lived optically excited triplet states instead of stable radicals as source of electron polarization practically eliminates the main path of nuclear spin lattice relaxation. Using triplet DNP the protons in a pentacene doped naphthalene bulk single crystal have been polarized to a record value of 80% at a field of 0.36 T using a simple helium flow cryostat for cooling. This highly polarized sample has been kept at very moderate conditions of temperature around 80 K and magnetic field of 24 mT and transported to a neutron beam line without loss of polarization, where it served as a spin filter for polarization analysis in a neutron scattering experiment. Furthermore the polarized sample can be extracted from the DNP apparatus and stored and transported in a small holding magnet under liquid nitrogen.
DNP with Photo-excited Triplet Electron using Soluble Pentacene Derivatives

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DNP using non-thermalized electrons as a polarizing agent enables to overcome the limit, 660, of polarization enhancement ($\varepsilon$) of the conventional DNP using thermal electrons. The conventional DNP is carried out in the strong magnetic field and at cryogenic temperature to polarize electron spins in the order of 10%, however, DNP with electron spins in the photo-excited triplet state (Triplet-DNP) can achieve hyperpolarization independent of that conditions [1].

Pentacene is a de-facto standard polarizing agent in the Triplet-DNP. Its triplet state population is highly biased regardless of the temperature and the external magnetic field strength. In a single crystal of $p$-terphenyl, the electron spin polarization of pentacene is 73%, that is, the theoretical limit of the $\varepsilon$ can under some conditions exceed 1,000 for $^1$H spins. The triplet state has a lifetime of 20-100 $\mu$s (depend on the sublevel), which is long enough to be transferred to nuclear spins. $^1$H spins in a single crystal of $p$-terphenyl doped with pentacene was polarized to 34% at room temperature and in 0.4 T, which corresponded to $\varepsilon = 250,000$ [2].

In parallel, developments of Triplet-DNP for future chemical and biological applications have been conducted. $^1$H spin polarizations of 1.5% ($\varepsilon = 4,250$) and 0.7% ($\varepsilon = 1,900$) at 120 K and in 0.4 T using the glass samples of $o$-terphenyl and benzophenone doped with pentacene were realized [3]. $^{19}$F spins in 2,3,4-trifluorobenzoic acid and 5-fluorouracil co-doped into the above glasses were also polarized. Demonstration of Triplet-DNP in glass samples of organic solvents which are typically used in NMR spectroscopy is one of the next important steps, but pentacene’s insolvability and instability don’t allow us to proceed. This has seriously limited applicability of the Triplet-DNP.

In this poster, we present the first successful result of Triplet-DNP with a soluble pentacene derivative. We have examined solubility in several organic solvents and have measured VIS spectra in the solvents. Time-resolved ESR spectroscopy shows a large signal, comparable to that for pentacene. Finally, We succeeded in obtaining the enhancement factor $\varepsilon > 80$ for $^1$H spins using the glass of ethanol-$d_6$ : water = 90 : 10 (w/w) in 100 K and 0.67 T. This is the first demonstration of Triplet-DNP in the glass samples of the organic solvent that is typically used in NMR spectroscopy, and this result will open the way to the chemical and biological analyses with Triplet-DNP.

Nitrogen Vacancy (NV) centers in diamond are an attractive platform for dynamic nuclear polarization of nuclear spins, particularly because they are electronic spins that can be optically polarized at room temperature with modest laser powers. In the quest towards NV driven DNP, nanodiamond powder is particularly attractive: they have huge surface areas (>$6700 \text{ mm}^2/\text{mg}$ for 100nm particles), and one could arrange for a close physical contact between the polarized NVs and external nuclear spins.

Indeed the goal of optically “hyperpolarized nanodiamonds” has been a long-standing one; yet the strong orientational dependence of the spin-1 NV centers has remained challenging to surmount.

In this work, we overcome these challenges to optically hyperpolarize diamond powder, obtaining high bulk $^{13}$C polarization (>0.25%) comparable to the best results in single crystals [1]. We have developed a new, remarkably simple, low-field optical DNP technique that proves to be fully orientation independent. Our technique also allows simple control of the hyperpolarization direction, which only depends on the direction of microwave sweeps across the electron spectrum [2].

We have constructed a low-cost, portable, table-top micro-diamond “hyperpolarizer” that is capable of hyperpolarizing 5um diamond particles. The device also opens up several avenues for harnessing the biocompatible surface-functionalized nanodiamonds as MRI tracers.

Long-lived state of four spin system hyperpolarized at room temperature

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Dissolution Dynamic Nuclear Polarization (DNP) [1] conventionally using a cryogenic instrument is implemented for various biomedical applications. Recently, dissolution DNP at room temperature was demonstrated using triplet-DNP that utilizes photo-excited triplet electrons as polarizing agents [2]. This alternative technique saves cost and space of instruments and is expected to expand the applications of dissolution DNP. In some applications for investigation of long metabolic pathways and the in vivo imaging of metabolism, it is difficult to apply dissolution DNP owing to short spin-lattice relaxation time $T_1$. To improve the short lifetime of hyperpolarization, long-lived states, which have the longer polarization lifetimes $T_{LLS}$ than $T_1$, have been extensively studied [3]. Pileio, et al. have proved that a four spin system can have long-lived states experimentally [4].

In this work, we have highly polarized $p$-chlorobenzoic acid by using triplet-DNP. We have also implemented the long-lived state of the four $^1$H spin system of $p$-chlorobenzoic acid at benzene ring positions. The sample was prepared by dissolving 15 mg of $p$-chlorobenzoic acid and 50 mg of Sodium carbonate in 5 mL of D$_2$O (without degassing). We measured the $T_1$ and the $T_{LLS}$ of two singlet states of the four $^1$H spins of $p$-chlorobenzoate in solution. The obtained relaxation curves are shown in Fig. 1. The $T_{LLS}$ value for protons is about 13 sec. The $T_{LLS}$ value is around 3 times longer than the $T_1$ value. The obtained $^1$H spin polarization is 0.15 % for a powder sample doped with 0.04 mol % pentacene.

Figure 1: Saturation--recovery relaxation curves (open circles) and singlet relaxation curves (solid circles).

Nanoscale magnetic resonance imaging of intracellular proteins

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In situ measurement of distribution, structure and function of biomolecules in a cell is one of the ultimate goals in life sciences. Many approaches, including super-resolution fluorescence microscopy\cite{1}, electron microscopy\cite{2}, and correlative light and electron microscopy\cite{3}, have been made for nanoscale imaging in the cell. Compared to these techniques, magnetic resonance imaging has achieved great success due to its noninvasive, high tissue contrast and spatial resolving capabilities\cite{4}. However, conventional MRI techniques have their spatial resolution limited to a few micrometres\cite{5} and hence are unable to resolve the intracellular bio-molecules at subcellular level. To overcome this limitation and demonstrate nanoscale MRI of intracellular proteins in situ, we employ an atomic-size quantum sensor based on nitrogen-vacancy centre in diamond. The native ferritins were imaged at \(~10\) nanometre spatial resolution by scanning the quantum sensor over the cross section of HepG2 cell. Correlative MRI and electron microscopy of sequential sections confirm the magnetic spin signal indeed comes from ferritin clusters in the cytoplasm. The approach paves the path to label-free single molecular MRI of intracellular proteins and their correlative ultrastructural context.

Wide-band microwave magnetometry using a nitrogen vacancy center in diamond

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We experimentally demonstrated a wide-band microwave magnetometry with an off-resonance protocol based on the Bloch-Siegert shift effect. Compared with the on-resonance method such as Rabi oscillations, the off-resonance microwave magnetic field accumulates quantum phase on the quantum superposition state by Bloch-Siegert shift effect, resulting in a great increase of the response bandwidth. We experimentally verified this enhancement and studied the optimization of the protocol to achieve an increase in frequency bandwidth by an order of magnitude compared to the Rabi method. In addition, the microwave frequency was extracted with a two-qubit system. The new approach enables the building of broadband microwave magnetometer for more realistic experiment condition to allow various potential application.
100-Fold $^{13}$C DNP Enhancement in Diamond Nanopowder at 9 T

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Naturally occurring defect centres in diamond, such as the NV centre and the P1 centre have been explored in the past as endogenous hyperpolarizing agents for $^{13}$C DNP in bulk diamond. Large enhancements have been observed by others for micropowders [1]. However, DNP has not yet been reported in nanometre sized particles at high field. We present $^{13}$C DNP enhancements of up to 100 in powders of 20 nm mean size using a home-built static DNP NMR spectrometer at 9 T.

DNP enhancements as shown (above left) were all obtained with a build-up time of 10 s, which is less than the time needed for complete recovery of the hyperpolarised signal at 20 K and 60 K. The enhancement at 20 K increases with increasing build-up time, up to a value of 100 at 60 s.

Using up to 60 W of microwave power, we were able to obtain DNP at temperatures from 20 K to 300 K. Dielectric heating at such high powers was avoided using a planar NMR probe specially designed for this purpose [2]. EPR spectra were taken in house at 9 T (above right). Comparison with the frequency dependence of the DNP enhancement indicates a complex interplay of DNP mechanisms. The increase of enhancement with build-up time (not shown) indicates a multi-exponential nuclear $T_1$ relaxation.

Exploiting endogenous paramagnetic surface defects for the direct dynamic nuclear polarization of micro/nanocrystals of silicon and diamonds

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Dynamic nuclear polarization (DNP) relies on the transfer of angular momentum from highly polarized electron spins to the surrounding nuclear spins. In most cases, the source of unpaired electrons comes from the doping of the sample with exogenous radicals such as TEMPO or Trityl, mixed in a glassing solution [1]. However, crystals of elemental silicon or carbon (diamonds) exhibit naturally occurring surface defects [2]–[6] which can be used to polarize 29Si/13C nuclei within the crystalline core. In particular, crystalline silicon and diamonds in the form of micro and nanoparticles are attractive targets for hyperpolarization due to their ability to store the enhanced nuclear polarization for an extensive period of time owing to a very long $T_1$ relaxation time (~ tens of minutes). Such hyperpolarized micro/nanoparticles offer potentially a broad range of applications as background-free contrast agents for biomedical imaging in MR [7], [8], with a much longer lifetime than any other hyperpolarized molecular probes reported so far [9].

In this communication, the possibility to exploit endogenous surface defects in micro and nanocrystals of silicon and diamonds for direct DNP will be discussed. In particular, various material properties that affect achievable polarization levels and rates, such as particle size, concentration of the defects and relaxation properties, will be described. The extension to the in-vivo applications with hyperpolarized nanocrystals will be demonstrated with the examples of g.i. tract imaging in mice.

Mesoscopic magnetic resonance spectroscopy with a remote spin sensor

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As one of the most important techniques, magnetic resonance spectroscopy finds broad applications in chemistry, biology and material science. Nanoscale magnetic resonance based on optical detection of electron spin resonance of nitrogen-vacancy (NV) centers in diamond has recently received broad attention in the context of quantum sensing. Magnetic resonance spectroscopy with nanoscale organic samples [1-3] and single molecules [4, 5] have been realized. Until now, the majority of nanoscale experiments measured a statistical fluctuation magnetization of spins which is much stronger than the mean thermal magnetization ($M_z \propto B_0/T$) with a nano-detection volume under the ambient conditions with the magnetic field of several hundred gauss. However, the fluctuation signal reduces dramatically with increased distance between the NV sensor and the sample.

For the mesoscale quantum sensing, e.g., cellular-sized magnetic resonance, the thermal polarization magnetization is stronger than the fluctuation. Additionally, higher polarization can be achieved via hyperpolarization approaches such as optically induced polarization [6], dynamic nuclear polarization (DNP) [7-9], and quantum-rotor-induced polarization [10, 11]. The polarization signal can be dominant once the spin polarization $P$ is reasonably high (normally, $P \sim 10^{-2}$ for electron spins and $\sim 10^{-4}$ for nuclear spins) even for the nanoscale sensing.

Here we report a long-range sensing method by detecting the spin polarization, so that mesoscale sensing based on NV center can be realized. This spin polarization removes the power law dependence on the separation distance between the target ensemble and the NV sensor. To demonstrate the method, we detect the mean magnetic field created by optically polarized electron spins within a pentacene-doped crystal. The optically induced polarization is improved a thousandfold compared to the calculated thermal polarization at ~500 G. This results in three orders of magnitude signal enhancement. With this method, we can detect the magnetic resonance spectra and measure its two typical decay times of the pentacene molecules doped in a crystal with the size of a few tens of micrometers. The long-range sensing method paves the way for mesoscopic quantum sensing in chemistry, biology and material science at ambient conditions.

We developed a Dynamic Nuclear Polarization (DNP) system, which is based on a commercial X-band Electron Spin Resonance spectrometer. ESR bridge was modified for handling high-power microwave, produced by 15 W amplifier externally mounted. Cryostat installed in cavity can lower sample temperature down to 3.3 K. Electromagnet can generate magnetic fields up to 0.65T. RF coil wound in ENDOR cavity is used for in-site monitoring of NMR signal enhancement via solid-state DNP.[1]

Hyperpolarized nanodiamonds (ND) are promising imaging agent, having surface functionality, decent hyperpolarization efficiency, and relatively long T1 relaxation time.[2] In this work, hyperpolarization study of ND was conducted at 0.32 T and 3.3 K with the X-band DNP polarizer. ND samples are commercially available, having a mean diameter of 250 nm. Polarization time was measured to be around 20 s. DNP spectrum exhibited two peaks separated by around 0.4 mT, corresponding to 11 MHz. This indicates that solid effect mechanism seems to be still dominant in hyperpolarizing ND at 0.3 T region. The dependence of microwave power was also measured for optimizing DNP condition. The hyperpolarized ND showed over 7000 fold enhancement in 13C NMR signal at 0.32 T and room temperature.

Overhauser Dynamic Nuclear Polarization at Nearly Zero Magnetic Field

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It’s been expected\cite{1} and verified\cite{2} that, below 1 mT, the efficiency of Overhauser Dynamic Nuclear Polarization (O-DNP) significantly decreases, which, in turn, diminishes the usefulness of O-DNP when one needs hyperpolarization at nearly zero fields. Such efficiency drop stems from the concurrent of positive and negative enhancements of NMR signal, since linearly polarized RF excites both transitions simultaneously.

We experimentally prove that O-DNP can be conducted at virtually zero magnetic field. Hyperfine coupling in Nitroxide radical is essential and dominant when magnetic field is nearly zero. Circularly Polarized RF, instead of linearly polarized one, induces only one of the positive and negative transitions. The selection is purely determined by the orientation of the circularity. With two RF coils orthogonally oriented and a phase synchronized two-channel RF source, in-phase and quadrature RF field can be produced at sample space. SQUID(Superconducting Quantum Interference Device)-detected NMR system was used. In reducing magnetic field from 7 μT down to 2 nT, the NMR signal intensity enhanced with circularly polarized RF nearly remains unchanged, while that enhanced with linearly polarized RF becomes 1000 times less.

Our results conclude that O-DNP with circularly polarized RF can an efficient hyperpolarization method at nearly zero magnetic fields. Limitations and improvements will be discussed.

Magnetic resonance (MR) is one of the most important techniques for characterizing compositions, structure and dynamics of molecules. Over the past several years, quantum sensing with Nitrogen-Vacancy (NV) center has opened a new door for magnetic resonance spectroscopy of a single molecule. In my talk, I will mainly introduce several new experimental results on both of methods and biology applications. (I) Zero-field electron spin resonance (ESR) spectroscopy on nanoscale. We successfully measured the zero-field ESR spectrum of a few electron spins, by precisely tune the energy levels of NV centers to be resonant with the target spins, and directly resolved the hyperfine coupling constant. This work break the sensitivity limitation and open the door of practical applications of the zero-field ESR. (II) ESR spectroscopy of single molecules under physiological conditions. The work represents a step forward towards magnetic resonance investigation of biomolecules in their native environments at the single-molecule level.

Dark matter searches via ultralow-field nuclear magnetic resonance (CASPER)

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The nature of dark matter, the invisible substance that makes up over 4/5 of the matter in the universe, is one of the most intriguing mysteries of modern physics. Elucidating the nature of dark matter would profoundly impact our understanding of cosmology and particle physics.

Recent theories of couplings between dark matter and nuclear spins have opened the possibility of directly detecting axion, axion-like and dark-photon dark matter via NMR spectroscopy [1]: as nuclear spins move through the galactic dark-matter halo, the spins couple to dark-matter particles and behave as if they were in an oscillating magnetic field, potentially generating a dark-matter-driven NMR signal. The Cosmic Axion Spin Precession Experiment (CASPER) is multi-faceted NMR search for such particles [2]. Here, we will review a CASPER experiment based on zero- to ultralow-field NMR (ZULF NMR).

We first review the physical principles enabling the detection of dark-matter via ZULF NMR and introduce the off-resonance-based measurement scheme used for such detection. We then describe the current ZULF NMR apparatus and present an exotic data processing scheme, which enables the possibility to perform coherent averaging of transient NMR signals induced by sources of unknown frequencies such as dark matter. Finally we show how recent NMR hyperpolarization schemes such as parahydrogen-induced hyperpolarization and signal amplification by reversible exchange will allow this experiment to probe uncharted territories, digging deeper in physics beyond the Standard Model.

Highly sensitive magnetometers play an important role not only in the fundamental physics [1], but also in the medical science [2]. In the biomagnetic measurement, a superconducting quantum interference device (SQUID) is employed as the magnetometer [3]. Recently, optical magnetometers have been developed [4]. The optical magnetometer relies on the interaction between an alkali atom whose spin is polarized by the optical pumping and an applied magnetic field. A field sensitivity of the optical magnetometer is comparable to the SQUID and it can be operated without a cooling system required by the SQUID. We are developing the optical magnetometer based on the nonlinear magneto-optical rotation (NMOR) effect [5] of Rb atom toward the magnetoencephalography and the search for the violation of the fundamental symmetry in the particle physics.

In the NMOR-based magnetometer, the magnetic field is measured by monitoring the polarization plane rotation of the linear polarized light that interacts with the Rb atom. The rotation angle of the light depends on the applied magnetic field. In order to reach the high field sensitivity, a long spin coherence time of Rb atom is needed. We prepared a Rb cell coated with an anti-relaxation material and a magnetic shield which suppressed effects of environmental fields. A three-axes Helmholtz coil was installed inside the shield to cancel out residual fields. The linear polarized light was supplied by a DFB laser. The laser light frequency was modulated to use the phase sensitive detection method. We studied the operation parameter dependences of the field sensitivity and demonstrated the field measurement. We will report the present status of the NMOR-based magnetometer and discuss the application of the magnetometer.

Development of a Rb Optical Magnetometer for Low Field NMR studies

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NMR signals are typically recorded at high magnetic fields by detecting the Larmor precession of the atomic nuclei inductively using pick up coils. The NMR spectrum is determined by the chemical shift dispersion of the atomic nuclei in such high field experiments. In contrast NMR spectrum at very low (below nT) external magnetic fields is dominated by the j- coupling interaction between the atomic nuclei in the sample. Inductive detection of signals at such low fields is made difficult as the induced emf in the pick coils is lowered by a factor of 10^5 or more due to the reduction in the Larmor precession rate. Optical magnetometers that detect the nuclear polarisation by non- inductive means are ideal sensors for low field NMR as has been seen in recent experiments [see for example 1/ 3]. The optical rotation of a linearly polarised probe laser beam passing through a gas of alkali atoms is a sensitive measure of the local nuclear polarisation, through its affects on the electron polarisation of the alkali atoms.

In this presentation I will describe the efforts of our group in building a Rb optical magnetometer. We use the linear and nonlinear Faraday effect to sense the local fields that are calibrated with solenoid coils. We employ techniques based on the concept of weak measurement to enhance the sensitivity of the magnetometer to optical rotation and are able to measure changes of 0.6nT in the local field.

References:
I describe two novel methods for the production of spin-polarized atoms and molecules, through the UV and IR optical excitation of molecules:

First, the UV photodissociation of hydrogen-isotope halides (e.g. HCl, DI), with circularly polarized light, can produce, at first, highly electron-spin-polarized H/D atoms [1,2,3,4]. Subsequently, the electron polarization is transferred to the nuclei and back via the hyperfine interaction, in ~1 ns. We measure these hyperfine quantum beats of the electron magnetization using a pick-up coil, for pulsed H and D densities of $10^{19}$ cm$^{-3}$ [5], which is about 6 orders of magnitude higher than those produced by conventional continuous-production Stern-Gerlach or optical-pumping methods. We characterize the depolarization, through a DI-D intermediate species, which helps explain the unusually long polarization lifetime of ~10 ns and the saturation of the depolarization rate at high pressures. I discuss proposals, based on this method, for measuring polarized laser fusion of D-T, D-$^3$He, and D-D reactions [4], and for producing spin-polarized molecules through chemical reactions.

Second, the IR rovibrational pulsed-excitation of molecules, with circularly polarized light, followed by the hyperfine interaction, produces spin-polarized nuclei, after an optimal time delay, typically on the $\mu$s time scale [6,7,8,9]. The nuclear polarization can be isolated in the nuclei, by terminating the hyperfine beating, either by photodissociating the molecules or trapping them at surfaces.

LOD-ESR investigation of Trityl doped $^{129}\text{Xe}$ DNP samples at 6.7 T and 1.1 K

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Alternatively to the well-established hyperpolarization method Spin Exchange Optical Pumping (SEOP), sublimation-DNP offers the advantage of employing non-dedicated hardware and perspectives of potentially higher throughput [1], but, so far, at lower polarization level. Addressing the challenge of homogenously embedding solid $^{129}\text{Xe}$ into a TEMPO radical-doped glassing matrix, Capozzi et al. [2] demonstrated a tradeoff between incorporable quantity of gas and achievable polarization: solvents able to incorporate a higher Xe concentration were the ones providing lower DNP performances because of the larger $^1\text{H}$ nuclei concentration in the glassing matrix.

In the present study, we investigate the performances of Trityl radicals for $^{129}\text{Xe}$ DNP at 6.7 T and 1.1 K. Trityl radicals are well acknowledged in dDNP for providing high $^{13}\text{C}$ polarization because of their ESR line width smaller than $^1\text{H}$ Larmor frequency, in same conditions of field and temperature [3]. The values of $^{13}\text{C}$ and $^{129}\text{Xe}$ gyromagnetic ratio are very close, nevertheless Trityl radicals failed in polarizing $^{129}\text{Xe}$ at significantly high levels [4]. We have performed LOD-ESR measurements on two samples (a and b respectively) doped with 30 mM Finland trityl Acid form (5M Xe dissolved in isobutanol and isobutanol only, see Fig 1A) to understand if the presence of Xe in the matrix affects the radical properties. Not only incorporating the gas modified the appearance of the ESR spectrum, but also reduced the electron T1 by a factor 3. This was not the case when TEMPO was employed as polarizing agent (data not shown). Moreover we measured the DNP spectra of $^{129}\text{Xe}$, in sample a, and of $^{13}\text{C}$ in a control sample containing [1-$^{13}\text{C}$]pyruvic acid + 30mM Trityl (see Fig 1A and 1B). The asymmetry observed in the first case could be an indication of poor Xe solubility in the matrix at these high concentrations of Trityl. Further experiments are needed to explain how it might contribute to the poor DNP performances we observed.

Figure 1. LOD-ESR spectrum and microwave DNP sweeps for $^{129}\text{Xe}$ dissolved in isobutanol + 30mM Trityl (left) and [1-$^{13}\text{C}$]pyruvic acid + 30mM Trityl (right) at 6.7 T and 1.1 K.

BOOSTING $^{129}$Xe DNP EFFICIENCY USING ULTRASONIC SAMPLE MIXING AND MICROWAVE FREQUENCY MODULATION

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The unique properties of Hyperpolarized (HP) $^{129}$Xe provide a highly sensitive tool for probing the local environment. HP $^{129}$Xe has been extensively used to study materials or for biomedical MRI including functional imaging of the human lung or brain [1][2]. Alternatively to the well-established hyperpolarization method Spin Exchange Optical Pumping (SEOP), sublimation-DNP offers the advantage of employing non-dedicated hardware and perspectives of potentially higher throughput [3,4]. Nevertheless, the challenges of homogeneously embedding solid $^{129}$Xe into a radical-doped glassing matrix [5] and the consequently lower nuclear polarization levels achieved prevented sublimation-DNP from spreading across the hyperpolarization community. In the present work we propose an improved sample preparation and the use of microwave modulation to enhance DNP performances in a system characterized by poor electron spin spectral diffusion [6].

Sample homogeneity was improved by using ultra-sonication instead of magnetic stirring. All measurements were performed at 5 T and 1.5 K on a sample containing 5M Xe dissolved in 50 mM TEMPO-doped isobutanol. The microwave irradiation frequency was set to 139.9 GHz, which corresponds to the maximum positive DNP enhancement.

Modulating the output frequency of the microwave source (ELVA-1 VCOM-06/140/1/50-DD) by means of a sinusoidal function showed a strong dependence of the DNP performances on the sinusoid’s amplitude (see Fig. 1, modulation frequency fixed at 10 kHz). In optimal conditions (44 MHz modulation amplitude) the enhancement was improved by a factor 2.5. Furthermore, the build-up time was reduced by 25% independent of the modulation amplitude. Moreover, the new sample preparation procedure employing ultrasonic waves guaranteed more reproducible results and further increased the polarization levels achieved.

The unreactive, ionizing radiation-free nature of hyperpolarised $^{129}$Xe facilitates repeatable, well-tolerated clinical imaging of pulmonary structure and ventilation [1, 2] where traditional proton MRI techniques are ineffective due to the inherently low proton density. This facilitates more reliable diagnosis and treatment efficacy for numerous disorders, including asthma, Chronic Obstructive Pulmonary Disease (COPD) and Idiopathic Pulmonary Fibrosis (IPF). $^{129}$Xe hyperpolarisation can be performed via Spin-Exchange Optical Pumping (SEOP), whereby angular momentum is transferred from circularly polarised resonant photons to $^{129}$Xe atoms, using electronic spins of a vapourized alkali metal such as rubidium or caesium as an intermediary. A nitrogen buffer gas is used to perform collisional quenching, preventing radiation trapping and helping to maintain long-lived $^{129}$Xe polarisations.

In contrast to the majority of clinical work performed using continuous flow processes in more stable, low Xe density regimes, we seek to maximize available magnetisation using stopped flow methods in Xe-rich gas mixtures [3], with $^{129}$Xe typically comprising between 10 and 80% of the total pressure. More reliable characterisation of this regime is key to understanding the co-dependence of temperature, alkali metal vapour density and other variables in an attempt to both maximise observed signal-to-noise ratios and maintain stable, long-lived polarisation for use in clinical imaging.

This characterisation is performed via a combination of parallel techniques – NMR spectroscopy is used to determine the net nuclear spin polarisation of $^{129}$Xe, whilst atomic absorption spectroscopy allows determination of the alkali metal vapour density. Additionally, Raman spectroscopy facilitates rotational temperature measurements of the nitrogen buffer gas, providing a unique understanding of thermal convection and transport processes within the optical cell where direct temperature measurements using in situ or surface thermocouples are impractical to undertake, or do not accurately portray the dynamics involved. It has been reported previously that temperature elevation may be on the order of or exceed 100 °C at the cell centre relative to the surrounding oven and cell wall [4, 5]. Using the described methodology, three avenues of investigation are pursued – the effect of mass flow on Rb-$^{129}$Xe SEOP during build-up and subsequent relaxation, the effect of a thermally conductive He buffer gas on Rb-$^{129}$Xe SEOP temperature dynamics and resulting thermal runaway, and for the first time, a comparison of Rb-$^{129}$Xe SEOP and Cs-$^{129}$Xe SEOP using broadband and frequency-narrowed pump lasers.

Method for fast, efficient and continuous application of hyperpolarized $^{129}$Xe in aqueous and biocompatible liquids

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Modern, clinical, radiological diagnostics increasingly require contrast agents that bind specifically to special molecular target structures (e.g., a tumor antigen) to identify and treat diseases in the early stage (e.g., metastases) or to control therapies minimally invasive. This concept is also called “molecular imaging” because the contrast agents react on certain molecules only and therefore need to be detected in such small (molecular) amounts [1].

NMR with hyperpolarized (HP) substances is one potential candidate for such molecular imaging strategies. However, the contrast agents have to be functionalized and hyperpolarized for this purpose. One promising idea is to use HP-Xe inside functionalized host molecules as proposed in [2]. Here the sensitivity stems from the HP-Xe while the selectivity is realized by the sensitive chemical shift of xenon even to small changes of the electronic structure of the host. Functionalizing this container with one or more targeting structures allows then the study of metabolic processes e.g. the binding of the functional group to one or more enzymes.

A critical issue for real applications is the solution of the HP-gas in the liquid which contains the host. Ideally this process must be fast, efficient and preserve the polarization. About a decade ago we suggested to mimic the function of the lung by using hollow fiber membranes (from commercial heart-lung machines) for this, which additionally have the great advantages that they are already approved for clinical use and prevent the formation of foams [3]. This idea was later also applied for in-vivo studies by Möller et al. [4].

Recently we have started to optimize applications via these hollow fiber membranes even further. Different types of compressors were tested in terms of function and useful materials. Special emphasis was put on systematic improvement of transfer losses in the gas and in the liquid phase. Furthermore, the storage of the HP-Xe, during the long experiments, could be improved by new concepts [5]. This ultimately results in a high HP Xe polarization in the solute phase which was stable over 30 min and only limited by the size of the gas reservoir. The stability of this approach was finally demonstrated on 2D NMR experiments of HP-Xe in water-soluble cryptophane-A (Cr222 (OCH2COOH)6) [6].

The efficiency of heat and mass transfer has a profound impact on the activity of catalyst and the overall productivity of chemical reactors that utilize gas flow and permeation through a porous solids. The pressure and temperature in these systems is often such that gas density is low and diffusion is within the Knudsen regime (i.e. diffusion in heterogeneous media with pore dimensions that are comparable or smaller than the mean free path of the diffusing particles). Hyperpolarization of xenon permits both structural and mass transport imaging, in particular for the study of low density and slow-moving gas transport in the Knudsen-regime that cannot be followed using other techniques [1].

To provide a better description of fluid flow in reactors, pore-scale lattice Boltzmann modelling (LBM) of axially symmetric H2O flow in a clear channel bound to a saturated porous medium was performed to match experimental velocimetry and dispersion maps [2]. Going beyond liquid flow, gaseous exchange in channels with porous walls that exhibit transverse permeability discontinuity in the otherwise Darcy flow was studied through Hp 129Xe velocimetry. We have localized gas flow through channels in minilith-type pellets and the permeation of gas into their porous walls. The impact of the gas permeation into the porous wall can be detected indirectly through deviations in the channel flow profile from Poiseuille flow, due to a lack of the no-slip boundary condition, and from direct imaging of permeating gas within the porous walls themselves.

The methodology was also applied to establish the structure-transport relationship in particulate filter that consist of hierarchical porous solids with ordered and disordered levels in the hierarchy. Hp gas phase MRI velocimetry allows to identify regions with dominant contribution to mass transport. Additional insights where obtained from the spin-lattice relaxation measurements with hyperpolarised 129Xe to probe the changing free pore volume at various water saturation levels that affect mass transport as observed in the 129Xe MRI dispersion maps. Three main step changes in T1 at free pore volume fractions where found during drying of the materials caused by the porous hierarchy and the data correlates well with complementary 1H and 2D relaxation measurements.

$^{3}$He and $^{129}$Xe Polarizers for Medical Applications

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The Metastability Exchange Optical Pumping process (MEOP) is usually performed at low magnetic field (~ mT) and low $^{3}$He gas pressure (1 mbar), which results in polarization exceeding 80%, but with a slow production rate. Moreover, for lung imaging, it is necessary to compress the helium gas to about 1 bar, without any polarization losses. The studies of the MEOP efficiency (characterized by the total magnetization and polarized $^{3}$He production rate) performed in the closed and open cells [1-3] motivated us to construct the polarizer working at elevated pressure in high magnetic field [4,5]. The idea was to quickly produce the polarized $^{3}$He gas in a compact polarizer (1.5 x 0.35 m) that fits inside the magnet of the most commonly used 1.5 T medical MRI scanner. The polarizer produces 600 cc of $^{3}$He gas of about 30% polarization in 40 minutes, enabling to obtain MR images of human lungs in vivo. In order to enhance the quantitative information in the human lung medical diagnostics, a dedicated ventilator has been recently implemented. It enables the precise measurement and control of gas delivery and the patient breathing processes, including the recovery of helium gas.

The $^{129}$Xe polarizer is based on the Spin Exchange Optical Pumping (SEOP). Rubidium vapor is pumped in the 1000 cc cell by a specially formed light beam of 8.5 W power. The narrow band VBG laser diode matrix is used. The regulated gas dosing system enables to apply various gas mixtures. For 2-3% Xenon concentration in the gas mixture we obtain polarization up to 55% (calibrated by comparing to thermally polarized water phantom). The hyperpolarized xenon is separated from the buffer gases (He, N2) in the nitrogen cold trap, which is located in the NdFeB Halbach magnet producing about 0.6 T.


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[1-13C]pyruvate hyperpolarized by means of d-DNP has been widely exploited for in vivo metabolic imaging studies [1]. Parahydrogen hyperpolarization of this substrate has been demonstrated through the so called PHIP-SAH method (Figure 1). In the proof-of-concept study [2] several issues (hyperpolarization level, bio-compatibility of product, concentration of HP substrate) had still to be solved in order to make the solution of HP pyruvate obtained through this method suitable for metabolic studies. In this work [3], the various steps of this method have been investigated in order to find the main experimental parameters whose optimization has to be pursued in order to increase the 13C polarization level on the final product. We report also about the studies that have been carried out to increase the concentration of the product in the water solution and to obtain a bio-compatible aqueous solution of the HP metabolite. Finally, HP [1-13C]pyruvate thus obtained has been applied in the investigation of the kinetics of the metabolic exchange of the 13C HP label with lactate on different cancer cells and in vivo. In the in vivo studies, slice-selective 13C-MR spectra have been acquired on mutant mice healthy and tumor-bearing mice using a 1T MRI system.

Figure 1. a) Scheme of the PHIP-SAH procedure: I) esterification of the carboxylate group with an unsaturated alcohol; II) hydrogenation of the unsaturated alcohol with para-enriched hydrogen; III) polarization transfer from the parahydrogen protons to the 13C carboxylate signal; IV) hydrolysis of the ester. The orange arrows indicate that these passages are carried out in an organic solvent, while the blue that the reaction occurs in an aqueous phase. B) series of 13C-NMR spectra acquired after perfusion of HP [1-13C]pyruvate through a suspension of 4T1 breast cancer cells.

References
Metal-Free Parahydrogen-Based Hyperpolarized Contrast Agents Produced via Rapid Catalyst Capture

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Hyperpolarization techniques based on the use of parahydrogen provide orders of magnitude signal enhancement for NMR and MRI. The main drawback limiting widespread applicability of parahydrogen-based techniques in biomedicine is the presence of organometallic compounds (the polarization transfer catalysts) in solution with hyperpolarized contrast agents. These catalysts are typically complexes of platinum-group metals and their administration in vivo should be avoided [1-4]. Herein, we show that a rapid (in less than 10 seconds) Ir-based catalyst ([Ir(IMes)H2S3]Cl (1), IMes = 1,3-bis(2,4,6-trimethyl-phenyl)imidazol-2-ylidene; COD = cyclooctadiene, S = pyridine) [5] capture by metal scavenging agents can produce pure parahydrogen-based hyperpolarized contrast agents as demonstrated by high-resolution NMR spectroscopy and inductively coupled plasma atomic emission spectroscopy (ICP-AES). The presented methodology enables fast and efficient means of producing pure hyperpolarized aqueous solutions for biomedical and other uses [6].

Figure 1. a) Chemical structures of metal scavengers used in the SABRE catalyst capturing studies. b) Concentration of Ir detected by ICP-AES after overnight storage of a 0.5 mL aqueous solution of 1 in the presence of different metal scavengers (10 mg). Scavengers’ identification (ID) numbers are listed in Figure 1a. Sample labeled X contained no scavenger. c) Concentration of Ir detected by ICP-AES after rapid capture (<10 s) of 1 from the 0.5 mL aqueous solution by different amount of the added metal scavenger (ID #3). Metal capturing efficiency is shown on the right.

Continuous Hyperpolarization with Parahydrogen in a Membrane Reactor


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Hyperpolarization methods entail a high potential to boost the sensitivity of NMR. Even though the “Signal Amplification by Reversible Exchange” (SABRE) approach uses para-enriched hydrogen, $p$-H$_2$, to repeatedly achieve high polarization levels on target molecules without altering their chemical structure, such studies are often limited to batch experiments in NMR tubes. Alternatively, this work introduces a continuous flow setup including a membrane reactor for the $p$-H$_2$ supply and consecutive detection in a 1 T NMR spectrometer. Two SABRE substrates pyridine and nicotinamide were hyperpolarized, and more than 1000-fold signal-enhancement was found. Our strategy combines low-field NMR spectrometry and a membrane flow reactor. This enables precise control of the experimental conditions such as liquid and gas pressures, and volume flow for ensuring repeatable maximum polarization.

FIELD SWEPT POLARIZATION TRANSFER IN PARAHYDROGEN NMR


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Much work in the field of parahydrogen-enhanced NMR involves the transfer of proton polarization to heteronuclei using the molecular J-coupling network. Techniques such as magnetic field cycling [1] and ‘SABRE-SHEATH’ [2] have emerged for this purpose. Both techniques work by exploiting avoided state crossings at ultra-low magnetic fields.

We present a surprising new discovery: If a molecule containing a heteronuclear spin is parahydrogenated at some magnetic field to yield an AA’X spin system, and the field is adiabatically swept through the zero point and up in the opposite direction, the parahydrogen singlet order is transformed into magnetization on the heteronuclear spin.

To demonstrate this, experiments were performed in a ZULF (zero and ultralow field) NMR chamber (shown in Fig. 1), which afforded precise control over the magnetic fields applied to samples. Firstly, acetylene dicarboxylic acid was parahydrogenated to maleic acid. The field was then swept adiabatically from -2 to +2 μT to polarize the carbonyl 13C spin. The sample was then shuttled into a Magritek SpinSolve high field benchtop magnet for direct 13C detection. The result is shown in Fig. 2, alongside a comparison with a sample that did not undergo the field sweep.

We soon hope to employ this technique to hyperpolarize compounds in a continuous-flow manner.

1. F. Reineri et al, Nat. Commun., 2015, 6 5858

Figure 1: Schematic of the ZULF chamber, which is used to negate Earth’s field, and apply ultralow magnetic fields to the sample, prior to detection at high field.

Figure 2: Hyperpolarized 13C NMR spectra of maleic acid after performing the field sweep, and not. Without a field sweep, the net 13C polarization is zero, but by using the field sweep we are regularly achieving polarizations in the order of 1%.
SIGNAL ENHANCED MEDIUM FIELD NMR SPECTROSCOPY BY PARAHYDROGEN INDUCED POLARIZATION (PHIP)

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For chemical engineering purposes the application of benchtop NMR spectrometers is rapidly growing [1-2]. Compared to common high field NMR spectrometers medium field NMR spectrometers are flexible and easily applicable in every day laboratories because of their small size and no need of cryogenic media. However, limited sensitivity and chemical shift resolution are inherent drawbacks of medium field NMR spectrometers. When employing NMR spectroscopy under flow conditions the signal intensity further decreases because of incomplete premagnetization. This applies especially for nuclei with longer $T_1$ relaxation times (e.g. $^{13}$C). The combination of hyperpolarization techniques with medium field NMR spectroscopy directly overcomes the sensitivity issue even under flow conditions, since magnetization is created by the hyperpolarization method itself. By applying the easy to implement and very cost efficient hyperpolarization method PHIP the generated magnetization is independent from an exterior magnetic field in the case of ALTADENA (adiabatic longitudinal transport after dissociation engenders net alignment) experiments [3].

We present the evaluation of two setups for benchtop NMR, shake and continuous flow experiments, respectively. ALTADENA shake experiments are measured with a medium field NMR spectrometer on three different substrates (2-hydroxyethyl acrylate, 1-hexyne, and dimethyl acetylenedicarboxylate) in combination with appropriate solvents. Thereby, we address the question whether signal enhancement is accessible in $^1$H as well as in $^{13}$C spectra in medium field NMR measurements on various substrates and to which extent. The hydrogenation of HEA is chosen for continuous flow measurements. For these experiments a flow setup is implemented at the benchtop NMR spectrometer where a membrane module based on hollow semipermeable fiber membranes is used to bring gas and liquid into contact [4]. Using water as well as D$_2$O as solvent the time dependent signal intensity of the reaction product is measured and the reaction kinetics is deduced.

The results show that the shake experiments have resulted in significant NMR signal enhancements of several ten thousand both on $^1$H as well as on $^{13}$C nuclei. Especially the results for $^{13}$C PHIP spectra are a huge benefit, since the acquisition of $^{13}$C with high SNR is impossible at medium field in diluted non-isotopically enriched samples within a reasonable acquisition time. Continuous flow experiments with PHIP allow a measurement of reaction kinetics during flow. Here as well PHIP has proven to be an enabling technology.

**TIME-RESOLVED NUS INTERLEAVED ACQUISITION ON BENCHTOP SPECTROMETER UNDER PHIP CONDITION IN A CONTINUOUS FLOW SYSTEM**

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Cost-efficient benchtop NMR spectrometers are increasingly used in industry (e.g. real-time monitoring of hydrogenation reactions). However, despite many technological improvements they still suffer on poor chemical shift dispersion and low sensitivity, which result from relatively low magnetic field strength. Parahydrogen induced hyperpolarization (PHIP) methods offer strong NMR signal enhancement and could be an asset in benchtop NMR spectrometers. The peak overlap problem can be solved by applying 2D spectroscopy, optionally further improved by NUS.

Therefore, the aim of a presented work is to adapt technique known as TR-NUS [1] (time-resolved non-uniform sampling) combined with interleaved acquisition to monitor para-hydrogenation reaction by 1D and 2D spectra simultaneously.

Data acquisition is accomplished by recording 1D spectrum and two NUS points of indirect dimension in a loop. Obtained stack of NUS points is thereafter divided into overlapping subsets of the same size and each of them is reconstructed using CS algorithms [2]. As a result, one can obtain set of 2D and 1D spectra with good temporal resolution. The experiments were performed on Magritek Carbon 43MHz spectrometer. The hydrogenation reaction was conducted in earth magnetic field by constantly bubbling parahydrogen (50%) in a chemical reactor. Reaction mixture was continuously pumped through spectrometer flow cell in a closed circuit.

Described method gives great insight into PHIP experiment and may be useful when hydrogenation occurs for a mixture of substrates. Moreover, the acquisition of 1D spectra in a interleaved manner enables to track experimental setup stability. Therefore, potentially disturbed 2D points can be localised and excluded or corrected.

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The hyperpolarization technique SABRE (Signal Amplification By Reversible Exchange [1]) is of interest because it is cheap, rapid, scalable, and easy to perform; moreover, unlike “traditional” parahydrogen-induced polarization (PHIP), SABRE does not irreversibly alter the substrate. Many of our efforts are directed at current limitations of SABRE: For example, to broaden SABRE applicability we are investigating cleavable “double agents” [2] comprised of one moiety that reversibly binds SABRE catalysts, and a payload moiety (in analogy to recent PHIP results [3]); following SABRE hyperpolarization (facilitated by spin relay [4] within a micro-Tesla field [5]) and rapid hydrolysis, two hyperpolarized (HP) species are created—a pH-sensing agent and a metabolic agent (e.g. $^{15}$N-imidazole and $^{13}$C-acetic acid, respectively). Towards the creation of catalyst-free HP agents, we are pursuing both heterogeneous catalysts [6] and catalyst-immobilization strategies [7], and obtained $^{15}$N polarizations of the potential hypoxia sensor metronidazole [8] of ~34% [7].

Recent efforts in SEOP (spin-exchange optical pumping) concern the use of in situ low-field NMR and optically-detected ESR (e.g. [9]) to probe stopped-flow SEOP of Xe at clinically relevant scales. One effort is to measure fundamental parameters governing Xe SEOP under these demanding conditions (e.g. spin-exchange and spin-destruction rates), as well as studying how different experimental variables (including laser technology/power, temperature, gas densities, and alkali metal choice) affect SEOP efficiency for $^{129}$Xe and $^{131}$Xe. For $^{129}$Xe, we are interested in improving $^{129}$Xe hyperpolarizers [10], now leading to the 3rd-generation design. For the challenging quadrupolar isotope $^{131}$Xe ($I=3/2$) [11], one motivation is to increase the polarization and amount of HP $^{131}$Xe that can be prepared for possible use in polarized targets for neutron scattering experiments [12] that would test fundamental symmetries (e.g. time-reversal violations). Funding support: NSF CHE-1416268 & CHE-1416432, NIH 1R21EB020323 & R21CA220137, DOD CDMRP W81XWH-12-1-0159/BC112431, W81XWH-15-1-0271 & W81XWH-15-1-0272.

In this work we show that para-hydrogen induced polarisation (PHIP) can be implemented, and observed, on a single microfluidic device that integrates with a bespoke micro-NMR detector. This allows observation of molecules in μM concentrations in μL volumes. Our ultimate goal is to enable quantitative characterisation of metabolic processes in Lab-On-A-Chip cultures of cells, tissue slices, and small organisms.

Microfluidic systems operate on small volumes ranging from pico- to micro-litres. While miniaturised NMR detectors have good mass sensitivity at these size scales, their concentration sensitivity is still insufficient to observe many metabolites at physiological concentrations.

PHIP requires reaction of a suitable unsaturated substrate with parahydrogen gas. In the present work, we show that this can conveniently be achieved in a microfluidic system by allowing the hydrogen gas to permeate through a poly(dimethyl siloxane) (PDMS) membrane. In addition to demonstrating the PHIP effect, we present quantitative data on the reaction and transport kinetics, as well as the relevant spin relaxation times. The challenge here is two-fold: designing and fabricating a para-hydrogenation capable microfluidic device whilst integrating the device with a bespoke micro-NMR detector; and ensuring the hydrogenation, and transfer, of polarised product is sufficiently fast to observe PHIP.

While hyperpolarisation through membranes has been performed previously [1,2], our work integrates this with a microfluidic device compatible with an optimised probe with corresponding micro-NMR detector [3]. To this end, we have simulated the flow of reaction material and subsequent H2 depletion with the PDMS membrane(A); have verified the Ts of p-H2 is significantly long enough to be transported through PDMS without significant relaxation; used an analogous hydrogenation system (B) to successfully observed an ALTADENA signal with enhancement ~200 (C).

Carbenes - A novel group of molecules for the metal free activation of Parahydrogen?

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Parahydrogen Induced Polarisation (PHIP) is a well-established method for boosting the sensitivity of magnetic resonance for a broad range of applications. The observation of the enhanced NMR signals requires a break in the symmetry of the H$_2$-molecule, usually accomplished by the addition of para H$_2$ to a substrate of interest (hydrogenative PHIP) in the presence of a metal-based complex or nanoparticles as a catalyst. However, as the interaction of para H$_2$ with a metal center contributes to the relaxation of the singlet order, and to extend applicability of the technique, there has been growing interest in the investigation of metal-free substrates for the activation of para H$_2$.

To this end, the so-called frustrated (sterically separated) Lewis pairs (FLP) offer great potential for the design of metal-free catalysts, being able to split small molecules such as H$_2$ and CO. The applicability to PHIP experiments has already been demonstrated for different FLP-type compounds, including molecular tweezers like ansa-aminoboranes and triphosphabenzene.

Cyclic (alkyl)amino carbenes (CAAC) are another promising group of molecules since they possess a lone pair of electrons together with an accessible vacant orbital (Fig. 1), and, hence, mimicking a transition metal centre. The addition of H$_2$ to these carbene centres has already been demonstrated by Frey et al. in 2007. However, to our knowledge, there are no studies involving the utilisation of PHIP techniques.

Here, we report preliminary investigation on the use of CAACs for PHIP experiments, including their preparation and reactivity towards H$_2$. These studies could provide further insight to the mechanism of H$_2$ splitting at a carbene centre with an electronic singlet state configuration. Furthermore, the characterisation of the spin dynamics in the hyperpolarised reaction product would greatly support the development of a new route for the metal-free activation of para H$_2$.

Hyperpolarisation on Tap – Towards the construction of a continuous-flow polariser for the production of hyperpolarised metabolites

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The development of hyperpolarised metabolites, such as pyruvate and lactate, greatly boosts the sensitivity of medical MRI techniques, improving the clinical applicability of those methods e.g. for cancer imaging and enabling new fields of application [1,2]. Up to now, most of the existing methods and commercially available devices for hyperpolarised MRI targets utilise the Dynamic Nuclear Polarisation (DNP) method, requiring large and expensive instrumentation [3]. Moreover, these devices work in batch mode, solely generating a single plug of hyperpolarised material at one time. For clinical applications, however, a continuous flow would be advantageous, as it can be easily integrated into clinical molecular imaging procedures, allowing for lower concentrations of metabolites to be injected at once and signal averaging over longer periods of time. To this end, we are aiming to develop a novel apparatus, for generating hyperpolarised substances “on tap”. The “Hyperpolarisation on Tap” (HoT) polariser combines the well-established concept of side-arm hydrogenation (SAH) PHIP [4,5] with a new approach for transferring the polarisation in a continuous-flow mode, involving a hydrogenation reaction at ultra-low magnetic field followed by a field reversal step sweeping through zero. Here, we present the initial design and technical specifications of the HoT-polariser along with preliminary data of the field-sweep polarisation transfer experiments.

Ultrafast 2D NMR analysis of SABRE-hyperpolarised mixtures


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Signal amplification by reversible exchange (SABRE) is a promising hyperpolarisation method using parahydrogen to enhance the sensitivity of NMR experiments. However, SABRE-hyperpolarised NMR signals are short lived, particularly when $^1$H is concerned, and therefore SABRE is often used to record 1D NMR spectra only. Recording 2D spectra would indeed require several scans with a high reproducibility, which is experimentally demanding and not appropriate when the analysed sample evolves. For a complex mixture, this may result in severe spectral overlaps. Here, we describe approaches combining the concepts of SABRE-hyperpolarisation [1] and spatially-encoded NMR [2] to obtain clean and sensitive 2D COSY [3] and DOSY [4,5] spectra of mixtures of small molecules in a single scan. These schemes, respectively displayed on the left and right parts of the Figure, can be used for fast separation of components in a mixture.

Anti-phase spin order of H$_2$ in high-field experiments with parahydrogen and its manifestations in SABRE-derived polarization

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Recently some of us have found that the $^1$H NMR signal of dissolved molecular hydrogen enriched in parahydrogen (pH$_2$) exhibits in the presence of an organometallic hydrogenation catalyst a completely unexpected, partially negative line shape [1]. Detailed analysis shows that it results from a strongly enhanced two-spin order connected to the population of the T$_0$ level of orthohydrogen (oH$_2$). Thus, the spin order of H$_2$ is altered: it is no longer the singlet order but anti-phase order. We have discovered that singlet-T$_0$ mixing in H$_2$ strongly affects SABRE (Signal Amplification By Reversible Exchange) polarization generated at high fields. First, we are able to elucidate the previously unknown mechanism of spontaneous polarization transfer in such experiments [2]. Specifically, polarization transfer goes in three steps: (i) singlet-T$_0$ mixing in catalyst-bound H$_2$; (ii) formation of net polarization of H$_2$ due to cross-correlated relaxation; (iii) polarization transfer to the SABRE substrate, occurring due to the nuclear Overhauser effect. The proposed mechanism is supported by a theoretical treatment, magnetic field-dependent studies and high-field NMR measurements with both pH$_2$ and thermally polarized H$_2$. Second, we demonstrate that variation of the spin order of H$_2$ requires modification of NMR methods used in high-field SABRE [3]. Specifically, methods proposed for the initial singlet order may fail once singlet-T$_0$ mixing comes into play; however, a simple modification makes them efficient again. Additional gain in signal enhancement can be obtained by using re-polarization, i.e., by repetitive polarization transfer using selective NMR excitation [4]. Hence, for efficient use of SABRE one should note that polarization formation is a complex multi-stage process: careful optimization of this process may not only deal with chemical aspects but also with the spin dynamics, including the spin dynamics of H$_2$.

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Over 60% $^{13}$C polarization by pulsed Para-Hydrogen Induced Polarization and Sidearm Hydrogenation

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Hyperpolarization has been proven to be one of the solutions to intrinsically low sensitivity of magnetic resonance (MR). Its methods like Dynamic Nuclear Polarization (DNP) opened the possibility to obtain $^{13}$C hyperpolarized metabolites and contrast agents and thus to investigate their transformation in vivo, as their $T_1$ times are usually longer than those of hydrogen. Thus, diagnostic applications of MR are broadened not only in vitro but also in vivo. One of the limitations of DNP are the costs of polarizers and need for cryogenic temperatures, which hinders rapid development of hyperpolarized methods in medicine. Another way of hyperpolarization is the Parahydrogen Induced Polarization (PHIP) that is a chemistry-based technique; it is easier to handle, cost effective, and allows much shorter polarization times. Proton polarization on the order of unity can be achieved. However, a drawback of this technique is the small number of molecules for which unsaturated precursors are available. Thus, only few biomolecules were polarized by parahydrogenation. One option to overcome this is PHIP-SAH (PHIP by means of sidearm hydrogenation). Here, a metabolite is functionalized by moieties that can be hydrogenated and proton polarization stemming from parahydrogen is transferred to the biomolecule’s $^{13}$C nucleus. Subsequent detaching of the hydrogenated moiety, for example by hydrolysis, allows to get pure hyperpolarized metabolites. The efficiency of the polarization transfer is crucial for the whole technique.

Here we aim for polarization transfer using the newly invented NMR pulse sequence ESOTHERIC (Efficient Spin Order Transfer to HEteronuclei via Relayed INEPT Chains). By hydrogenating 1-$^{13}$C-vinylacetate-d$_6$ followed by subsequent polarization transfer from two-spin longitudinal order (from parahydrogen originating protons) to the carbonyl $^{13}$C moiety of acetate (in the reaction product ethyl acetate), results in 60% polarization. Transfer can also be done in two steps, first from hyperpolarized protons to the carbon of a side arm and then to carbon of interest in a metabolite. In the later case, hyperpolarization is accomplished by developing an isotopic labelling strategy for generating precursors containing a favourable nuclear spin system to add para-hydrogen and convert its two-spin longitudinal order into enhanced metabolite signals. Our technique provides a fast way of generating hyperpolarized metabolites using para-hydrogen directly in a high magnetic field where all spins are weakly coupled, achieving $^{13}$C signal enhancements up to 100,000-fold ($B_0 = 7T$) and without the need of field cycling.

Hyperpolarized $^{13}$C pyruvate is widely used for investigations and imaging of metabolism and other biological processes. Currently dynamic nuclear polarization is the polarization method of choice, but we aim to hyperpolarize $^{1-13}$C pyruvate and $^{1-13}$C acetate using parahydrogen induced polarization (PHIP), following the approach pioneered by the group of Aime [1]. This would provide a cheaper and faster route to polarizing the substances.

We use radiofrequency polarization transfer techniques to transfer spin order of an added parahydrogen proton pair to a $^{13}$C site that has no direct J-coupling to the protons. This is done using a “bridging” nucleus in the molecule.

We achieved proton polarization transfer from the parahydrogen proton pair to a distant methyl $^{13}$C in methyl (methyl-$^{13}$C) maleate-$^{4-13}$C (see Figure 1a). Initially, proton polarization is transferred to the carbonyl $^{13}$C site using the S2hM sequence [2], then homonuclear polarization transfer is employed for further transfer from the carbonyl $^{13}$C to the methyl $^{13}$C. Figure 1b shows the result of applying this sequence to a parahydrogenated 10 mM dimethyl maleate in full natural abundance. The methyl $^{13}$C was polarized to ~2% which enabled us to detect the signal which originates from the ~2 $\mu$M molecules with two $^{13}$C spins, in 1 scan.

To form hyperpolarized pyruvate and acetate with high polarization levels, we are currently employing this technique on the molecules in Figure 1c. Preliminary data on this approach will be shown.

Figure 1: a) Transfer of parahydrogen singlet order into methyl $^{13}$C magnetization. The overall efficiency of this transfer is around 50%. b) Hyperpolarized $^{13}$C NMR spectrum of 10 mM dimethyl maleate in full natural abundance, at 11.7 T after parahydrogenating the precursor and performing the transfer sequence. The signal at 52.5 ppm originates from the ~2 $\mu$M molecules with two $^{13}$C spins in the positions of interest, from one scan. c) The molecules we are currently investigating, with the aim to produce hyperpolarized acetate and pyruvate.

A Pulsed PHIP Approach For Hyperpolarizing Metabolites

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Hyperpolarisation methods aim to enhance NMR signals by more than four orders of magnitude compared to those normally attained in typical laboratory conditions. Large signal enhancements allow for the development of novel diagnostic techniques, such as localized real-time observation of metabolic processes in vivo.\textsuperscript{[1]}

In para-hydrogen induced polarization (PHIP), pairwise addition of para-hydrogen to unsaturated bonds, usually mediated by a catalyst, dramatically enhances the \textsuperscript{1}H NMR signal originating from the hydrogenating protons.\textsuperscript{[2, 3]} PHIP methods cannot be directly applied to molecules lacking precursors with unsaturated bonds. The class of molecules to which PHIP can be applied has been extended by the introduction of para-hydrogen induced polarization by mean of a sidearm (PHIP-SA).\textsuperscript{[4]} In PHIP-SA, a sidearm with unsaturated bond is “para-hydrogenated”, the nascent polarization is transferred to a nuclear spin in a sidearm-bonded moiety and the hyperpolarized molecule of interest is released by cleavage of the sidearm.\textsuperscript{[4]}

Before cleavage, the polarization is usually stored as longitudinal magnetization in heteronuclei such as \textsuperscript{13}C or \textsuperscript{15}N, whose relaxation times can be several minutes long.

Here we demonstrate a pulsed method for heteronuclear polarization transfer in PHIP. The method is based on a sequence for the Efficient Spin Order Transfer to HEteronuclei via Relayed Inept Chains (ESOTHERIC).\textsuperscript{[5]} The sequence is designed for transferring para-hydrogen spin order to in-phase heteronuclear magnetization, ready for the direct manipulation or polarization storage in the PASEDENA version of PHIP. It is shown that the sequence can transfer the full longitudinal para-hydrogen spin order in spin systems in which one of the $J$-couplings between the protons and the heteronuclear spin is much smaller than the other and that a minimum polarization transfer of 50\% is achieved when the two couplings are equal. The sequence allows a facile implementation, is offset independent and is robust with respect to pulse imperfections and incorrectly set timings.\textsuperscript{[5]}

In a series of PHIP experiments, the achievement of high heteronuclear polarization levels is demonstrated directly in the field generated by the magnet, without the need of field cycling. With an excellent reproducibility, we report above 95\% of spin order transfer efficiency in metabolite precursors, with close to 60\% polarization levels in metabolite precursors and up to 20\% polarization in the corresponding cleaved metabolites.\textsuperscript{[5, 6]}

\textsuperscript{[6]} S. Korchak, S. Mamone, S. Glöggler, submitted.
HYPERPOLARIZED ULTRAFAST LAPLACE NMR

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NMR relaxation and diffusion measurements provide detailed information about dynamics and structures of substances such as porous materials, and reveal interactions of nuclei with their microscopic environment. Since relaxation and diffusion data comprise exponentially decaying components, the processing requires a Laplace inversion in order to extract the diffusion coefficient and relaxation time distributions. Thus, these methods are referred to as Laplace NMR (LNMR). [1]

Multidimensional approach increases the chemical resolution of an NMR experiment. Multidimensional and even some 1D experiments are time consuming, since the experiment needs to be repeated several times with varying evolution delay or gradient strength to gain proper multidimensional data. This restricts the applicability of multidimensional LNMR methods and is considered general problem of multidimensional NMR. In many cases it prevents the use of hyperpolarized substances for signal amplification. This problem can be tackled by introducing spatial encoding of two-dimensional data, as was originally done in ultrafast NMR spectroscopy [2,3] and later in ultrafast multidimensional LNMR [4-6]. The price to pay is reduced sensitivity. However, the single-scan approach enables the use of hyperpolarization (e.g. PHIP, DNP [5] and SEOP [6]), which provide much higher sensitivity boost than the loss due to spatial encoding.

In this presentation we introduce the principles of ultrafast multidimensional LNMR and the recent progress. We show that multidimensional LNMR experiments are able to increase chemical resolution to systems, which may lack it in traditional NMR spectra. We also demonstrate that, applying spatial encoding and hyperpolarization of many kinds, we are able to decrease the experimental time by many orders of magnitude and, at the same time, increase the sensitivity of the experiment significantly. The UFLNMR method also allows us to investigate dynamics of gases absorbed in porous structures which is not possible with ultrafast NMR spectroscopy.

ParaHydrogen Induced Polarization (PHIP) is a hyperpolarization technique that is known for its versatile application in analytical chemistry, catalysis and MR-imaging. PHIP is used to enhance the signals of $^1$H and heteronuclei. The PASADENA [1] experiment is probably one of the simplest and the most popular PHIP experiment because hydrogenation occurs in situ at a high magnetic field of NMR/MRI in a perfectly controlled environment (field, temperature, pressure, pH etc). Often, the PHIP signal is overlapping with or buried by thermal signal of reagents and solvents. To overcome this obstacle, various methods were developed. Recently, we revisited Only Para-hydrogen SpectroscopY (OPSY [2]) pulse techniques [under review].

We have shown that using OPSYd-111 (90X-(Gradient, 1$\tau$)-90X-(Gradient, 2$\tau$)) anti-phase PASADENA is robustly converted into in-phase polarization. Even though OPSYd-111 has significantly better performance than previously proposed methods, the amplitude of the total net signal is modulated by chemical shift difference. This is impractical when several species are polarized or the polarized system is unknown. Here, we present further modifications to OPSY in which the quantum coherences are refocused: Refocused OPSY with a zero-quantum selection filter (ROPSYz) and Double-Refocused OPSY with double-quantum selection filter (DROPSYd). These experiments remove the unwanted chemical shift modulation while maintaining the strong suppression of the thermal background signal.

DROPSYd provided the signal oscillation between total net magnetization and antiphase polarization as $\sim \sin(2\pi J\tau)$, where $J$ is the scalar proton-proton coupling. These new variants of OPSY significantly improve the representation of PASADENA signals and facilitates their quantification and analysis. In addition, the robust conversion of PASADENA signal to net magnetization in combination with the background suppression will enable an incorporation of these sequence elements in any imaging or spectroscopic methods.


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13C parahydrogen-induced polarization of acetates and pyruvates

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13C-hyperpolarized (HP) acetate and pyruvate can be used as contrast agents for MRI studies of tumor, brain and liver metabolism and other biomedical applications. Though protocol for hyperpolarization of these compounds using dissolution dynamic nuclear polarization (d-DNP) is well developed, the use of parahydrogen-induced polarization (PHIP) is promising due to its significantly lower cost and higher flexibility. PHIP is based on pairwise addition of two atoms from a parahydrogen (p-H2) molecule to the same asymmetric unsaturated substrate molecule. While acetate and pyruvate cannot be obtained by PHIP directly due to absence of corresponding unsaturated precursors, they can be hyperpolarized using PHIP side arm hydrogenation (SAH) approach [1]. The idea of PHIP SAH is to add p-H2 in a pairwise manner to unsaturated ester moiety and then transfer polarization to carboxyl 13C nuclei using magnetic field cycling (MFC). 13C HP acetate and pyruvate can be obtained by hydrolysis of resultant HP esters.

Herein, we report a systematic study of PHIP SAH of 13C-labelled and unlabelled ethyl, propyl and allyl acetates and pyruvates produced by homogeneous or heterogeneous hydrogenation of corresponding unsaturated precursors (vinyl, allyl and propargyl esters) with p-H2. 13C-labelled precursors (except vinyl pyruvate) were synthesized with the use of acetic and pyruvic acids as sources of 13C nuclei. Homogeneous hydrogenation in CD3OD yielded esters with pronounced hyperpolarization of 1H and 13C nuclei (the latter with the use of MFC). The highest polarization values were obtained for ethyl acetate (P13C = 4.7%) and allyl pyruvate (P13C = 5.4%, P1H = 31%), while for other compounds P13C were less than 1% [2]. Production of 13C HP ethyl acetate and allyl pyruvate was also demonstrated via aqueous phase hydrogenation of corresponding unsaturated precursors over water-soluble homogeneous catalyst with subsequent MFC. In this case, P13C = 2.1% for ethyl acetate and P13C = 1.0% for allyl pyruvate were observed. Feasibility of utilization of obtained HP esters for 13C MRI was demonstrated in vitro. Despite provision of high polarization levels, homogeneous hydrogenation has disadvantage of difficult catalyst separation from HP product. Thereby, we investigated the possibility of production of 13C HP esters via heterogeneous hydrogenation with p-H2 and MFC. Formation of 13C HP acetates was successfully observed in CD3OD and D2O solutions with P13C up to ~0.1%, while in the case of pyruvates it was not possible to detect 13C hyperpolarization, probably due to lower catalyst activity and competing side processes of C–O bond hydrogenolysis leading to hydrocarbons.

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[2] All presented in this abstract polarization values correspond to 85% p-H2 fraction.
Kinetics of spin order in SABRE systems at high-fields

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Signal Amplification by Reversible Exchange (SABRE) is a promising parahydrogen ($p$H\textsubscript{2}) based hyperpolarization technique which has been successfully used in recent years to archive high polarization in a variety of interesting target molecules. One limiting factor however is the need to construct, maintain and operate external polarizers and sample shuttling devices. We and others have worked on ways utilize the SABRE system directly in \textit{in situ} applications. In the case of SABRE at high fields, we have shown recently \cite{1} that the spin-order of free H\textsubscript{2} may be altered by exchange with the SABRE complex and its reaction intermediates which lead to rapid mixing of the singlet and central triplet states. This circumstance is a limiting factor for many previously suggested polarization schemes. Here we present a study of this spontaneously generated spin order by using a specifically designed pulse scheme in combination with a high pressure \textit{in situ} polarizer \cite{2} to obtain kinetics data. These data are fitted with a theoretical model based on our earlier work \cite{3}. In order to fit the experimental results obtained, our model treats chemical exchange between H\textsubscript{2}, the main SABRE complex and one reaction intermediate. Coherent and incoherent evolution, including CSA anisotropy and dipolar relaxation, are taken into account. With this line of investigation, we are able to ascertain the effects of the above mentioned parameters as well as that of the reaction intermediates on the spin order of H\textsubscript{2}. We are confident that this method will help significantly in the ongoing effort to establish SABRE as a routine high-field NMR and MRI modality by providing a means to study singlet-triplet mixing under various conditions and in different systems both experimentally and theoretically.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig1}
\caption{Experimental scheme (top) and example of the kinetics data showing double spin-order (red circles) being converted into in-phase magnetization (black squares) by cross-correlated CSA/DD relaxation. The data are fitted by the theoretical model developed (solid lines). Both the kinetics as well as the relative magnitude of generated spin orders are reproduced by the model.}
\end{figure}

\begin{thebibliography}{9}
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\end{thebibliography}
Para-hydrogen induced polarisation (PHIP) is a well-known hyperpolarisation technique which exploits the singlet state of $H_2$, known as para-hydrogen ($p$-H$_2$). The use of $p$-H$_2$ as a source of hyperpolarisation is an attractive one, as it provides a significant increase in NMR signal and is relatively easy and cheap to produce. In the original experiments of Bowers and Weitekamp $p$-H$_2$ was directly added to molecules via hydrogenation reactions, giving excellent signal enhancements but the target substrates for the technique were limited and the process was not reversible.[1] Signal amplification by reversible exchange (SABRE),[2] is a non-hydrogenative alternative which exploits the spin order of $p$-H$_2$ without incorporating it into the molecule. A metal catalyst is used to bring the $p$-H$_2$ into contact with a target substrate. Under the correct resonance conditions of coupling constants and magnetic field, the spin order from the $p$-H$_2$ can be transferred to the target substrate, which will subsequently dissociate allowing free substrate polarisation to be built up.[3] The only substrate requirement is the ability to bind weakly and reversibly to a metal catalyst. SABRE has attracted a lot of attention in the last decade due to its fast polarisation of the substrate (tens of seconds) and large signal enhancements which can be applied to a wide range of NMR applications which require greater sensitivity.

SABRE is of particular interest in improving the diagnostic capabilities of magnetic resonance imaging (MRI) in terms of monitoring metabolic pathways and in vivo probing of physiological processes. It can be easily applied to most spin $\frac{1}{2}$ nuclei including $^{31}$P, $^{13}$C, $^{15}$N and $^{19}$F. $^{19}$F is of particular interest as it is a spin $\frac{1}{2}$ nucleus, 100% abundant and has 83% of the sensitivity of $^1$H NMR. Here we analyse the viability of using $^{19}$F as a diagnostic tool in MRI. $^{19}$F is an interesting nucleus to investigate for MRI usage because has a very wide chemical shift range and it is not present in biological systems. Here, we focus on the SABRE polarisation of fluorinated $N$-heterocyclic compounds, discussing the effects of steric bulk, polarisation transfer field, pH and rate of ligand exchange on the observed SABRE response. We also present some $^{19}$F MRI results in phantoms, demonstrating possible use of $^{19}$F in MRI in the future. [4]

Nuclear Magnetic Resonance is currently being widely used for intensive investigation of complex molecular structures, in particular, peptides and proteins with important biological activities. However, Nuclear Magnetic Resonance suffers strongly from inherently low sensitivity which results from low polarization which strongly limits the further applications of MR – this is particularly true in the case of low concentrations. Therefore, since the early days of MR, the problem of low sensitivity has been addressed many times. A very promising approach which can help to overcome limitation of the low sensitivity is the so-called hyperpolarization technique, which can generate nuclear spin polarization that is far from a typical Boltzmann nuclear spin polarization. One of these techniques is Signal Amplification by Reversible Exchange, where the MR signal of molecules is enhanced by polarization transfer to molecules from a reservoir of high spin polarization which is stored in a hydrogen gas mixture enriched in parahydrogen (p-H₂). Until now, SABRE has been demonstrated for only a small number of biorelevant molecules. Furthermore, many important biorelevant molecular systems cannot be hyperpolarized via SABRE because of the lack of centers which are necessary for reversible interaction with p-H₂ and the catalyst. Thus, the proper design of SABRE-active substrates with biorelevant structures is currently of significant interest. Therefore, here, we will demonstrate that SABRE-activity can be induced into SABRE-inactive oligopeptides [1,2]. This can be done via a labelling procedure where a high SABRE-active unit is incorporated into the SABRE-inactive oligopeptides. In particular, in our presentation, we will discuss the interplay between labelled oligopeptide structures and SABRE activity. Finally, we will demonstrate that SABRE can enhance the NMR signal of peptide the Phe-Ala-Leu-Gly-Glu-Ala-NH₂ (FALGEA-NH₂) which is known as a very selective ligand towards EFGR (epidermal growth factor receptor) which regulates the growth of all cells originating from epithelium and are expressed in normal, healthy cells.

Forensic Hyperpolarization: Detecting Fentanyl and its Pyridyl Analogues

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In recent years there has been a striking increase in the prevalence of synthetic opiate consumption. In 2015, they were associated with 33,000 fatalities in the US alone, as opiate abuse reached epidemic levels. Fentanyl (fig. 1) is a prime example of this class of drugs: used recreationally for its euphoria-inducing effects, it is approximately 100x more potent than morphine. This is a serious threat to public health, as minute quantities of fentanyl (circa 2 milligrams) are enough to induce a fatal overdose. We therefore sought to polarise fentanyl in its free-base and hydrochloride salt forms, and its pyridyl derivatives using the hyperpolarisation technique SABRE (signal amplification by reversible exchange) [1] coupled with bench-top NMR in a move towards a forensic application. This technique enables the lethal dose of fentanyl to be detected in a single scan.

Figure 1: Chemical structure of fentanyl

The structure of fentanyl was chemically modified to incorporate a pyridine ring, by either replacing one of the phenyl rings or by modification of the amide. SABRE-RELAY [2] and conventional SABRE were utilized for the polarization of fentanyl (free-base and hydrochloride forms) and its derivatives. Exchange rate data was collected for the pyridine derivatives (hydride and fentanyl dissociation rates) in an effort to rationalize the hyperpolarization-based enhancement observed. We also demonstrate the forensic applicability, and selectivity, of this method by being able to polarize fentanyl only in a heroin / fentanyl mix.

The hyperpolarization of pyridine was firstly presented by Adams et al. in 2009 by using the so-called Signal Amplification By Reversible Exchange (SABRE) technique.[1] Since then, there have been far-reaching advances that are currently promising initial applications.[2] Data concerning the mechanism of spin transfer are rarely.[3] It is known that the chemical shifts, the scalar couplings of the active SABRE complex and the substituents of the ligands are important for the polarization transfer.[2,4] Therefore, we examine the influence of different substituents and their inductive effect (+I/-I) at the ligand system (see examples shown in figure 1).

The pyridine derivatives were dissolved in CD$_3$OD. In presence of the Ir-IMes-catalyst, the sample was degassed using argon and sonication. Hyperpolarization was realized with about 50% enriched para-H$_2$ and 6 bar pressure. The $^1$H, $^{13}$C or $^{19}$F NMR spectra were detected by using a single pulse experiment with a 90° excitation pulse on a Bruker WB-300 spectrometer. Effects on the pK$_a$ values, the signal enhancements and phases are observable.

Heterogeneous SABRE catalyst deactivation with resultant T$_1$ lengthening of the analyte

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Signal amplification by reversible exchange (SABRE), first reported in 2009 [1], allows for the creation of a hyperpolarised state in solution without the need for chemical change of the substrate. This has made SABRE an attractive technique for future medical imaging applications with magnetic resonance (MR) images of simple substrates already extant in literature; in addition to recent publications demonstrating the application of this technique to polarize world health organization essential medicines without modification [2].

However, there are still challenges to be overcome before SABRE is viable for in vivo imaging. One of these is the rapid relaxation of hyperpolarised spin states in proximity to the spin transfer catalyst used to facilitate substrate hyperpolarisation. This problem has been addressed previously to effect catalyst deactivation homogenously in solution in order to generate a hyperpolarised bolus with a commensurate T$_1$ to that of the substrate without the presence of the relaxing spin transfer catalyst [3]. However the most common of these spin transfer species, [Ir(IMes)(COD)Cl] [4], has recently been demonstrated to possess in vivo toxicity resulting in simultaneous homogenous catalyst and substrate injection being undesirable [5].

Therefore, in this work we present a novel methodology for lengthening substrate T$_1$ through heterogeneous catalyst deactivation, rapidly resulting in regeneration of T$_1$ values commensurate with the substrate alone. A range of suitable compounds for the application of this technique are presented in addition to a proposed mechanistic basis for the observed effect. We envisage this work could be applied to the rapid heterogeneous deactivation of the iridium species prior to injection for in vivo imaging, maximizing the T$_1$ of the substrate and mitigating catalyst related toxicity concerns.

NMR is an excellent, albeit inherently insensitive analytical technique whose signal arises from the population difference between the spin states as dictated by the Boltzmann Distribution.[1] This sensitivity can be increased through hyperpolarisation methods which show a significant deviation in the population of states, away from the Boltzmann distribution.[2] Here we highlight the parahydrogen based hyperpolarisation method; signal amplification by reversible exchange (SABRE) which exploits the singlet state of hydrogen, parahydrogen and an iridium metal catalyst for the enhanced detection of a target molecule (substrate). The substrate and parahydrogen are brought together via the temporary formation of a scalar coupled network facilitated by the metal catalyst which allows the spin order of parahydrogen to be transferred to the substrate.[3] The hyperpolarised substrate then dissociates from the metal centre into the bulk solution, resulting in a build-up of hyperpolarised signal.

SABRE targets are typically pyridine derivatives containing a nitrogen atom which is capable of ‘soft’ binding to the iridium SABRE catalyst. Here, we demonstrate that this association is influenced by the pKₐ of the nitrogen centre. As the pKₐ increases, the association becomes stronger. This results in slower substrate dissociation, due to the higher ligand loss barrier (ΔG°₆). Additionally, the catalyst contributes towards relaxation, hence the stronger the association, the faster the rate of relaxation (T₁). Relaxation destroys hyperpolarisation therefore substrates which form strong associations provide low enhancements. This is also observed for weak associations where substrate dissociation is too fast to allow for sufficient polarisation to be transferred to the substrate.

These differences have been analysed for the substrate series; 4-chloropyridine, 4-methylpyridine, 3-methoxypyridine and 4-pyridinecarboxaldehyde. In the case of 4-methylpyridine, polarisation levels of 3% were achieved. These results are rate dependent according to the earlier hypothesis.

Quantitative NMR analysis at nanomolar concentrations via Para-Hydrogen Induced Hyperpolarization.


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Nuclear spin hyperpolarization (e.g., Dynamic Nuclear Polarization (DNP), Para-Hydrogen Induced Polarization (PHIP), etc.) has gained a widespread interest over the last years as a tool to enhance NMR sensitivity. Particularly, SABRE is a hyperpolarization technique based on the reversible association of substrate molecules and parahydrogen (p-H₂) to an iridium complex in solution. At low magnetic field, a transient scalar coupling network within this complex allows the spontaneous transfer of spin-order from p-H₂ to the nuclear spin of the substrate molecules. By rapidly shuttling the hyperpolarized sample to high magnetic field, NMR signals enhanced up to three orders of magnitude compared to thermal equilibrium conditions can be detected.

Here, we present a novel high-field PHIP approach that can be applied to highly complex mixtures, such as biofluids and natural extracts. The proposed approach is based on the reversible association of SABRE substrates to an iridium catalyst that acts as an NMR chemosensor, allowing the selective detection of target compounds (down to nanomolar concentrations) while removing the large background originating from the complex matrix. We have recently applied this technique to complex mixtures, such as urine solid phase extracts, in which hundreds SABRE substrates at low- or sub-micromolar concentrations could be simultaneously detected. A method for fast quantitative analysis of these PHIP NMR spectra will be presented.
Cyclic coherent hyperpolarisation of water with pH2

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In biomolecular NMR, hyperpolarised water could offer an enormous potential. Water is compatible with almost any biological and clinical applications and its protons are possibly a generalizable source of hyperpolarisation. Para-Hydrogen (pH2) could provide a very attractive approach for hyperpolarisation of water. Theory has indicated that catalytic hydrogenation of compounds containing X->O semi-polar bonds (e.g. N2O, C5H5NO or Ph3PO) with pH2 might provide pathways to generate hyperpolarised or even para-water. Both the Wilkinson catalyst [(Ph3P)3RhCl] or, alternatively, a palladium cis-dihydride species have been suggested for this purpose, but it has never been realised experimentally.[1,2]

Combining a classical SABRE catalyst IrCl(COD)(limes) with amino propyl diethoxy methyl silane dissolved in methanol allowed to hyperpolarise water with pH2. After contact with pH2 at low field, the phase of the CD3OH/H2O peak at 4.8 ppm was inverted (Figure 1). Varying the contact time with pH2, the build-up of polarisation continued up to 70s and remained constant up to 120s before a slow, gradual decrease in polarisation was observed (Figure 1).

The coherent transfer of magnetisation immediately indicates water as the hyperpolarised species and excluding D3COH/HOD for which incoherent polarisation transfer from pH2 has previously been reported.[3]

The exact mechanism of polarisation transfer, either SABRE type, concerted double proton exchange or a combination thereof is currently unknown. Concerted double proton exchange is known in asymmetric hydrosilylation reactions using iridium catalysts.[4] In this case, two silane molecules and water convert to a disiloxane, generating H2. The reverse reaction could serve to perform coherent transfer of polarisation from parahydrogen:

\[ \text{R}_3\text{SiOSiR}_3 + \text{IrH}_2 \rightarrow \text{Ir(SiR}_3)_2 + \text{H}_2 \text{O} \]  
\[ \text{Eq. 1} \]

CONTINUOUS FLOW SABRE POLARIZATION FOR NUCLEAR MAGNETIC RESONANCE AND NUCLEAR SPIN-INDUCED MAGNETO-OPTIC EXPERIMENTS

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Nuclear magneto-optic spectroscopy (NMOS) is a young field of research studying effects based on interaction between nuclear spin magnetization and light radiation mediated by the molecular electron cloud. The simultaneous influence of optical excitations and localized magnetic fields from aligned nuclear spins gives rise to intrinsic, molecule-specific optical responses, such as linear or circular birefringence. While NMOS phenomena are closely related to NMR observables, such as chemical shifts and dipolar couplings, the presence of perturbation by the light also brings in additional information about electronic structure. The only experimentally observed NMOS effect is the so-called nuclear spin-induced optical rotation (NSOR) [1], but the efforts have so-far dealt mostly with pure substances, such as neat solvents, or binary mixtures of compounds, both of which were present in appreciable fractional amounts of tens of percent. In addition to NSOR, several other NMOS phenomena have been theoretically predicted [2], but not experimentally observed. As with the NMR, one of the main experimental concerns is the low spin polarization leading to low sensitivity.

We report a system that uses para-H$_2$ and SABRE method [3] to produce continuous supply of polarized sample and flow it through the bore of an NMR magnet or NMOS cell for measurements. As a demonstration we present the comparison of NMR spectra of pyridine polarized either thermally or using our setup, showing successful continuous hyperpolarization of the sample and great increase in signal intensity. We also report our findings on the imaging capabilities of the flowing liquids in our system. Furthermore, the combination of a solution-based continuous hyperpolarization technique with the NMOS instrumentation allows observation of NSOR of samples in sub-molar concentrations with the signal quality comparable to that of neat liquids investigated in previous studies, bringing it closer to chemically relevant conditions and significantly widening the pool of viable samples.


BULK NUCLEAR HYPERPOLARIZATION OF INORGANIC SOLIDS

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MAS DNP can be used to hyperpolarize the bulk of organic solids, given that spontaneous \(^1\text{H}-^1\text{H}\) spin diffusion transports magnetization generated at the surface into the particle. We report a strategy for hyperpolarizing inorganic proton-free materials, using incipient wetness impregnation and spin diffusion among heteronuclei. Multiple cross-polarization contacts are used to transfer hyperpolarization from protons in a radical containing wetting phase to heteronuclei at the surface of the material. Provided that heteronuclear T\(_1\) values are long, even slow spin diffusion from surface to bulk can result in spectra with better sensitivity than is obtained with conventional solid-state NMR. We show how a factor 50 gain in overall sensitivity of the \(^{119}\text{Sn}\) spectrum of SnO\(_2\) can be achieved using this method. Spin diffusion is also observed among \(^{31}\text{P}\) nuclei in GaP, \(^{113}\text{Cd}\) in CdTe and \(^{29}\text{Si}\) in SiO\(_2\) (\(\alpha\)-quartz).

Figure 1. Left: DNP enhanced CP-MAS \(^{119}\text{Sn}\) spectra of SnO\(_2\) impregnated with 16 mM TEKPol in tetrachloroethane, showing spin diffusion among tin nuclei. Right: Schematic representation of hyperpolarization of proton-free inorganic bulk.
SOLIDS DNP OF INSENSITIVE NUCLEI AND CHALLENGING MATERIALS

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We will discuss solids DNP approaches to quickly detect the NMR signals of insensitive nuclei, such as the ones with low natural abundance (e.g. $^{17}$O, 0.037 %) [1,2] or with small magnetic moments (e.g. $^{89}$Y) [3], and illustrate how these can be exploited to address some fundamental issues in materials chemistry (e.g supramolecular assemblies [4,5], heterogeneous catalysis).

We will show how natural abundance $^{17}$O NMR of solids can be obtained in minutes at both 9.4 and 18.8 T with MAS DNP at low temperatures. While the Overhauser polarisation transfer scheme (with the solid particles incorporated into a glassy o-terphenyl matrix doped with BDPA) yields larger signal enhancement factor at 18.8 T than the cross effect mechanism (enabled by TEKPol biradical in oxygen-free 1,1,2,2-tetrachloroethane solution), the latter sample formulation provides a more time efficient data acquisition approach at both 9.4 and 18.8 T. The results open up a powerful method for rapidly acquiring high signal-to-noise ratio solid-state NMR spectra of $^{17}$O and to probe sites on or near the surface, without the need for isotope labelling.

We will also show that cross effect DNP at 9.4 T permits the fast acquisition of the NMR spectra of low gyromagnetic ratio nuclei such as $^{89}$Y ($\gamma(^{89}\text{Y}) = \gamma(^{1}\text{H})/20$). The detection of the $^{89}$Y NMR signals from hydrated yttrium doped zirconates [6], in combination with DFT calculations, allows the local yttrium (and proton) environments present in these important protonic conductors to be detected and rationalised.

Finally, we will present structural insights in challenging supramolecular assemblies and heterogeneous catalysts systems that have been enabled by cross effect DNP.

Solid-state NMR spectroscopy provides unique information on the atomic-level structure of hybrid materials. However, the lack of sensitivity of this technique poses major limit for the detection of surface sites, diluted species or insensitive isotopes (\(^{15}\text{N}, \, ^{17}\text{O} \ldots\)). In recent years, it has been shown that DNP represents a promising approach to address this issue since it can enhance the sensitivity of NMR experiments by one to three orders of magnitude at \(B_0\) up 21.1 T and under Magic-Angle Spinning (MAS).

We demonstrate here for the first time how DNP can enhance the signal of Dissolved Organic Matter (DOM) [1]. We measure significant DNP enhancement, even if these natural samples, collected from Siberine rivers, are complex mixture of organic molecules and contain endogeneous paramagnetic species, which can decrease the efficiency of the DNP transfer. The sensitivity gain provided by DNP permit us to probe \(^{13}\text{C}-^{27}\text{Al} \) proximities in DOM and to show the complexation of \(\text{Al}^{3+} \) ions by DOM carbonyl sites.

DNP-NMR also provides new insights into the structure and the reactivity of bio-inspired heterogeneous catalysts, made by controlled calcination of periodic mesoporous organosilicates. DNP allows detecting the carboxylic groups at their surface and their reaction with amine to form covalent bonds in water at room temperature.

Through these examples, we also discuss future challenges for the DNP-NMR characterization of hybrid materials.

Dynamic nuclear polarisation enhanced solid-state NMR studies of catalytic materials and small organic molecules.

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Dynamic nuclear polarization (DNP)\(^1,2\) gives large signal enhancements in solid-state NMR (ssNMR) spectra via the transfer of spin polarisation from unpaired electrons from radicals implanted in the sample. This implies that apart from the bulk signals that are already obtained with conventional ssNMR, signals from dilute species betokening the alteration of the surface can be studied within a reasonable amount of time\(^3\).

In this work we describe two different kinds of systems: (a) DNP-enhanced ssNMR study of the widely used catalyst \(\gamma\)-alumina which is often modified at the surface by the incorporation of alkaline earth oxides in order to control the availability of catalytically active penta-coordinate surface Al sites\(^4\), and (b) small organic molecules which acts as pharmaceutical drugs, such as naloxone and derivatives, knowledge of whose structure is very important to have the correct conformation as active pharmaceutical ingredient (API).

For the study of \(\gamma\)-Al\(_2\)O\(_3\) and its modifications we will present 1Ds showing the modification of surface species along with 2D MQMAS data showing the isotropic shifts of the relevant species with their quadrupolar parameters and chemical shift information.

For the study of organic molecules, we will present 2D through-bond\(^5\) and through-space\(^6\) correlations aimed at corroborating and/or finding the conformation of these kind of molecules and relating their structural differences to their differential functions as APIs.

References
The characterization of the architecture materials on the nanoscale is of great importance today.

However in many cases, where the sample is either opaque or made of many mixed components such as pharmaceutical formulations, determining nano structures still remains an unsolved analytical problem. Since there are very few direct methods to probe the inside of these types of materials, solid-state NMR is an attractive approach to look at these structures in their solid-state.

Here we show how, combined with a model for $^1$H spin diffusion, DNP NMR can be applied to determine domain sizes in tailor-made core shell nanoparticles. Using an approach where we selectively dope the nanoparticles by impregnating the material with a radical containing solution, we show by comparing saturation-recovery DNP enhanced CPMAS experiments and numerical simulations how the core and shell enhancements are characteristic of the core radius and the shell thickness of the nanoparticle, as shown in Figure 1.

![Figure 1: Left: SEM image of the core-shell nanoparticle before impregnation. Right: $^{13}$C CPMAS enhancements as a function of polarization delay of polystyrene particles coated with mesoporous silica containing CTAB impregnated with 12 mM of the biradical AMUPol in $^{13}$C-glycerol-d$_2$/D$_2$O/H$_2$O (6/3/1) recorded at 9.4 T, 100 K and 12.5 kHz MAS. Circles represent experimental measurements, while solid lines represent numerical simulations of spin diffusion.](image-url)
Surface structural study of N-doped Hydrothermal Carbon (N-HTC) by Isotopic Enrichment and DNP-SENS (Dynamic Nuclear Polarization Surface-Enhanced NMR Spectroscopy)

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Hydrothermal Carbon (HTC) derived from biomass is a class of low cost, environmentally friendly functional materials with many potential applications such as catalysts, absorber, electrode, etc. In particular, nitrogen-doped carbon materials (N-HTC, Figure 1a, [1]) are beginning to play an important role in energy conversion and storage technologies like water splitting and fuel cell applications. Understanding the surface structure of N-HTC is important when applying N-HTC as an electrode for water splitting because all reactions take place on the surface of the materials. In this work, N-HTCs were specifically synthesized by glucose and urotropine as precursors to achieve a particular content of nitrogen in the material.

Isotopic 13C and 15N enrichment (selectively and fully) in combination with DNP-enhanced NMR spectroscopy are used to determine the synthesis mechanism and the detailed surface structure of N-HTC. From the interaction study between solvents and N-HTC by NMR, the proper condition of the radical ‘juice’ was found. The incipient wetness impregnation technique (IWI) was used, aiming at a uniform wetting of the surface to enable DNP-SENS [2]. Even though the BET surface area of N-HTC is very low (~ 0.7 m²g⁻¹), the sensitivity enhancement provided by DNP is essential for providing information on the atomic level structure at the surface (ε = 14 for 15N-DPMAS, Figure 1b). In the case of a high urotropine content (Glu:Uro=1:4), the structure between bulk and surface seems to be homogeneous, while there is a pronounced structural difference for low urotropine content (Glu:Uro=1:0.17). In particular, urotropine has a greater effect on the surface structure formation than glucose.


Figure 1. a) N-HTC derived from glucose and urotropine, b) 15N DPMAS DNP

With MW (ε ≈ 14)
Dynamic nuclear polarization of Si microparticles using structural defects

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Dynamic nuclear polarization of powders most often involves wetting of the surface of the particles using exogenous radicals dissolved in a solvent. The radicals are used as the source for DNP enhancement of either the surface of the particles, or the bulk. Here, we study the surface of silicon microparticles by detecting 1H nuclei, known to only be found on their surface. We use defects that are intrinsic to the microparticles as a source of enhancement, thus not altering the surface with solvents or exogenous radicals — and importantly, not causing further oxidation and not adding more 1H nuclei into the sample. The surface protons consist of Si-H and Si-OH groups formed when water molecules oxidize the surface layer/s of the microparticles. Silicon microparticles attract a lot of interest in the scientific community because of their bio-compatibility and their potential as silicon-based bioMEMS (microelectromechanical systems) devices or for biomedical MRI, making understanding the oxidation/degradation of these materials very important.

This study involves an integrative approach that includes both static liquid Helium 1H-DNP and 1H- and 29Si-DNP using a commercial Bruker DNP-MAS spectrometer liquid Nitrogen temperatures. This work allows us to identify three different proton environments (previously these samples only showed a single 1H resonance). The proton environments are shown to be spatially separated from each other by use of solid-state NMR techniques such as CPMG and 1H hole-burning experiments. In static DNP we are able to change the microwave (MW) frequency in order to explore the full DNP spectrum (see Figure 1a). We also explore MW frequency modulation during the static DNP experiments as a possible technique to preferentially enhance one of proton over the other protons, effectively highlighting a specific spatial environment on the surface of these microparticles. Using MAS-DNP we explore the use of direct enhancement and 1H-29Si cross polarization (CP) as an additional way to better understand local spin ordering.

![Figure 1](image_url)

Figure 1: (a) DNP spectrum: NMR spectrum (x-axis) as a function of the MW frequency (y-axis) showing the enhancements of the different 1H resonances. (b-c) Comparison of the thermal NMR spectrum (red) and enhanced NMR spectrum (black) for (b) static DNP at 140MHz and 4.2K and (c) MAS-DNP at 600MHz and 100K (8kHz spinning frequency), illustrating that the surface protons are enhanced differently, therefore have different interactions with the defects.
Investigating small particles of organic powders using MAS dynamic nuclear polarization

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Solid state NMR (SSNMR) is a powerful technique to investigate samples that cannot be studied with traditional methods. For example, contrary to diffraction techniques, SSNMR can investigate small particles of powders with a diameter of less than 100 nm. Thanks to the sensitivity gain provided by MAS dynamic nuclear polarization, we will present how these small particles can be investigated with great accuracy, notably we will discuss the feasibility of one- and two-dimensional DNP experiments for the atomic-level characterization of the surface and bulk of powder samples obtained from different preparation schemes.[1]

Furthermore, we will present new polarizing agents that allow the structure of tiny particles of powders (< 10 nm) to be investigated with MAS DNP. This aspect is particularly interesting when metastable or intermediate polymorphs of organic molecules should be trapped and polarized.[2]

Figure 1: $^1$H-$^{13}$C HETCOR spectrum of a new metastable form of glycine recorded at 100 K and under microwave irradiation.


Alkaptonuria (AKU) is a rare disease due to a deficiency of homogentisate 1,2-dioxygenase on the tyrosine degradation pathway. Patients have an elevated plasma level of homogentisic acid (HGA) which accumulates over time in collagenous tissues, especially cartilage. HGA can polymerise into a dark pigment, and the darkly pigmented cartilage tissue shows drastic changes in mechanical properties giving rise to severe and early osteoarthritis. It is intriguing to understand how a relatively simple molecule such as HGA can lead to widespread changes in the biomechanical properties in the pigmented cartilage. Thus far, no animal or in vitro model can fully replicate the pigmentation process in the cartilage of human patients.

Using DNP-enhanced solid-state NMR, we carried out our study on human tissue obtained from joint replacement surgery. Pigmented and non-pigmented sections from the same patient were investigated. Using $^1$H-$^{13}$C NMR correlation spectra, we were able to attribute a low level signal in the aromatic region to the pigment species in the degraded cartilage from an AKU patient. Furthermore, hydrogen bond lengths in the collagen triple helix show a different distribution in pigmented cartilage compared to non-pigmented cartilage, indicating disruption to the cartilage extracellular matrix at the level within the collagen triple helix. Our study illustrates the potential of DNP-enhanced solid-state NMR to contribute to the study of biopsies and samples with medical and clinical relevance.
DNP polarization agents for the cellular milieu: new chemistries and approaches

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In recent years, there has been considerable interest in the use of dynamic nuclear polarization (DNP) and solid-state NMR for the structural studies of proteins in more native environments. This includes proteins embedded in native membranes or cell walls [1] as well as protein and protein assemblies present at low concentrations in cell lysates [2]. Extending this work to the cellular interior has been an exciting but challenging goal. One particular challenge is the stability of the current nitroxide-based biradicals in the reducing cellular environment. Another challenge is the lack of efficient strategies that allow the polarization and signal enhancement of only a specific protein target in the cell. We will present our progress on tackling these issues and the synthesis of polarization agents with novel properties for cellular structural biology applications in mind.

Cellular membrane disruption induced by the aggregation of amyloid beta (Aβ) peptide is considered a main mechanism responsible for neuronal death in Alzheimer’s disease. However, the molecular basis of this toxicity, in particular the interaction of Aβ and its aggregates with a cell membrane, remains unclear[1]. Solid-state NMR (ssNMR) is a very well suited technique for studies of the molecular basis of Aβ peptide interactions with cell membranes, but low sensitivity limits such studies due to a large fraction of the sample volume being taken up by lipids. Dynamic Nuclear Polarisation (DNP) allows increasing the signals in ssNMR experiments, thus enabling measurements with lower amounts of protein material[2]. In this work we explore the feasibility of structural ssNMR-DNP studies of Aβ(1-40) peptide, at low concentration, interacting with biomimetic lipid bilayers.

Aβ(1-40) peptide, uniformly labelled at specific amino acids, was pre-incorporated into buffered multilamellar vesicles consisting of the phospholipids 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) and 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-(1’-rac-glycerol) (POPG) in a 3:1 ratio. AMUPol polarizing agent and glycerol cryoprotectant were added to the sample to facilitate low temperature DNP. Experiments were carried out on an AVANCE III 600 MHz (1H lamor frequency) spectrometer with a 395 GHz gyrotron microwave source. 

13C signals were enhanced by a factor of 68 due to DNP as observed in 1H-13C cross-polarisation experiments. Two-dimensional 13C-13C (DARR) and 15N-13C (NCA, NCAX) correlation experiments were possible in under 3 hours at lipid-to-peptide ratio (L:P) of 20:1. In order to reduce the contribution of signals from natural abundance 13C of lipids we used double quantum (DQ) experiments. POST-C7 double-quantum single-quantum (DQSQ) correlation was shown to be feasible at L:P of 100:1 (70 nmol peptide) and 200:1 (35 nmol peptide) with well resolved cross-peaks in under 10 hours and under 20 hours, respectively. Secondary chemical shifts at the uniformly labelled amino acids in the Aβ(1-40) sequence agree with β-sheet conformation at these positions. This demonstrates that DNP enhanced ssNMR can be used to probe structures of Aβ(1-40) which exist at low concentrations L:P ratio in a cell membrane environment, which will lead to a better understanding of mechanism of cell disruption.

CONFORMATIONAL ENSEMBLES OF DISORDERED PROTEINS: 
A GLIMPSE INTO CHAOS AT HIGH SENSITIVITY

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We exploit high-resolution solid-state MAS NMR spectroscopy as well as DNP enhanced MAS NMR-spectroscopy for the study of structure and distribution of conformational ensembles of intrinsically unfolded as well as aggregated proteins. Low-temperature Nuclear Magnetic Resonance (NMR) spectra usually suffer from severe line broadening due to freezing out different conformations. While this is usually accounted for as an unwanted side-effect of DNP-NMR, inhomogeneously broadened lines also contain valuable information about conformational ensembles of (disordered) proteins as well as side-chain flexibility.

First, we studied the distribution of backbone conformations in the intrinsically disordered protein \( \alpha \)-syn in frozen solution in different states: the unstructured monomer, fibrillar \( \alpha \)-synuclein with flexible ends, and \( \alpha \) synuclein in contact with lipid bilayers [1,2]. We could probe the conformational ensembles of all valine residues in a selectively labeled sample of \( \alpha \)-syn by evaluating the inhomogeneously broadened line-shapes of the \( \text{Ca/C\textbeta} \) cross peak. 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 different protein to lipid ratios. Furthermore, secondary chemical shifts of neighboring amino acids tend to be correlated, indicative of formation of transient secondary structure elements. Our approach thus provides accurate quantitative information on the propensity to sample transient secondary structures in different functional states.

In a second attempt, we have investigated side chain conformations in a well-folded protein and studied the effect of unfolding on the rotameric ensembles of selected amino acid side-chains.

HIGH-RESOLUTION STRUCTURES OF MULTIPLE FOLDS ADOPTED BY GGGAGCG REPEAT RICH OLIGONUCLEOTIDES

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In the regulatory region of the human PLEKHG3 gene, which is expressed in many regions of the brain and represents a potential candidate contributing to the risk of autism, there are multiple GGGAGCG repeats. Different oligonucleotides from this region were extensively studied with the use of high-resolution NMR. A short oligonucleotide containing two such repeats d(GGGAGCGAGGGAGCG), VK1, was shown to fold into a tetrahelical structure very different from the two established tetrahelical families called G-quadruplexes and i-motifs [1]. Further studies have shown that a similar short oligonucleotide d(GCGAGGGGAGCGAGGG), VK34 folds into a unique tetrahelical structure that shares similarities with the VK1 structure [2]. By changing the nature of cations in solution we were able to also stabilize a tetrahelical VK34 structure. Additionally, longer constructs such as VK1-A-VK1 and VK34-A-VK34-A-VK34-A-VK34 folded into structures similar to VK1 and tetrameric VK34 structures, respectively. It remains to be determined what kind of folds will be preferred in oligonucleotides that contain multiple GGGAGCG repeats or even more importantly if such folds can be adopted in human cells. Sensitivity enhanced NMR techniques optimized for use with DNA molecules could be a powerful tool in determining what kind of folds are adopted by GGGAGCG-rich oligonucleotides inside human cells or in cell-like environments.

Figure 1: High resolution structures of VK1 (a), VK34 (b) and tetrameric VK34 (c) folds

In recent years, Dynamic Nuclear Polarization (DNP) has become a powerful tool for structural studies [1][2], with applications spanning from the solid-state NMR studies of proteins [1][3], to the development of heterogeneous catalysts [4][5]. However, despite its current widespread use, important questions remain unanswered regarding the exact location as well as polarization transfer specificity of a DNP radical for given macromolecular systems.

In our contribution we examine the influence of molecular size and proton density upon the resulting DNP efficiency and spatial polarization transfer specificity. We make use of AMUPol [6] as well as a taggable version thereof (AMUPol_MTSSL) we had introduced earlier [7]. We compare our experimental findings to theoretical studies using a classical spin diffusion approximation [8-10] as well as quantum-mechanical multi-electron-nuclear spin system calculations [11]. Finally, we introduce a novel approach to spatially localize DNP radicals in a macromolecular system.

Proton detected magic-angle spinning dynamic nuclear polarization NMR for the analysis of natural abundance biopolymers

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Structural analysis of proteins and other biomaterials in the solid-state has typically required extensive isotope labelling. However, with recent advances in dynamic nuclear polarization magic-angle spinning NMR it is now proving possible to study many isotopes without resort to labelling. Despite, its high natural abundance and favorable NMR properties few studies have been conducted that exploit the proton detected DNP which theoretically offers further significant improvements in sensitivity. Here we will demonstrate the feasibility of employing proton detected MAS-DNP to study the structure of unlabeled amyloid fibrils. DNP matrices that largely suppress the strong proton signals from the buffer will be presented, together with homonuclear decoupling schemes that improve the resolution of proton spectra at the low MAS frequencies that are currently available. We have utilized the enhanced sensitivity afforded by \textsuperscript{1}H detected MAS to obtain indirectly detected \textsuperscript{14}N spectra of \textbeta$_2$-microglobulin fibrils, exploiting the sensitivity of the second order isotropic quadrupolar shift to provide insights into the conformation of the proteins within the amyloid fibrils. In light of our findings, the merits of faster MAS and alternative DNP methods will be discussed.
19F Solid-State Dynamic Nuclear Polarization Enhanced NMR

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In the past, 19F Overhauser dynamic nuclear polarization (DNP) using nitroxide radicals has been used to study fluorinated aromatics and small molecules in solution at low magnetic field (0.3 - 3 T). With the introduction of high frequency microwave sources, stable nitroxide-based biradicals, and low temperature MAS probes, it is now possible to achieve large DNP enhancements at high magnetic fields in the solid-state. 19F DNP is relevant for the structure and dynamics characterization of many industrially relevant materials containing fluorinated compounds, including active pharmaceutical ingredients (API) where 20 to 25% of APIs contain at least one fluorine atom. We demonstrate that 8 mM AMUPOL in a trifluoroethanol-d3 glassy matrix (with microcrystalline KBr) provides significant 19F DNP enhancement at 9.4 T. We demonstrate 19F and 19F-13C cross polarization DNP enhanced NMR experiments for an impregnated microcrystalline sample of the API 5-fluorouracil obtaining enhancements in the bulk solid of 270 (Fig. 1). In addition, we measure the DNP enhancement in two dynamic regimes involving slow and fast rotation of the CF3 group in trifluoroethanol-d3.

Figure 1. 19F DNP enhanced NMR spectra of 5-fluouracil at 9.4 T impregnated with 8 mM AMUPol in deuterated trifluoroethanol with (black trace) and without (dashed trace) microwave irradiation acquired at 125 K, 12.5 kHz spinning speed, and using a 200 s recycle delay. The particular polymorph of 5-fluorouracil that we investigate here has more than one crystallographically distinct site.

In this work we present recent results of site-directed spin labeling on a protein to show the effect of the transition metal Gd(III) as a polarizing agent (PA) on the NMR properties a biological system. [1] Ubiquitin is a small, easy to handle, robust protein. The absence of cysteines allows for specific mutations for site-directed spin labeling. Therefore, ubiquitin is well suited as a biological model system.

We investigate the influence of varying levels of deuteration of ubiquitin on DNP. The results for different nuclei with varying effect on relaxation, enhancement and spin diffusion will be shown. By sweeping the magnetic field the solid effect matching condition can be chosen to specifically hyperpolarize hydrogen, carbon, or nitrogen, revealing large differences between the different nuclear types. While on carbon relatively small but significant enhancement factors on the order of ~10 are observed, this factor is boosted to over 100 on nitrogen. Uniformly across the nuclei build-up times increase for increasing levels of deuteration. Additionally, by comparing linewidths for different polarization periods and deuteration levels, we can follow the expanding range of hyperpolarization by spin diffusion. Finally, we deduce major contributions of this effects to the origin of methyl-induced $^{13}$C relaxation.

EFFICIENT SOLID-STATE DNP AT HIGH-FIELD, FAST-MAS AND HIGH TEMPERATURE: NARROW-LINE RADICALS AND THE ROLE OF SPIN DIFFUSION

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DNP is a powerful technique to boost sensitivity of MAS ssNMR by about 2 orders of magnitude and it is already significantly extending the application domain of ssNMR in material and life sciences. Nevertheless, the most efficient polarizing agents like the dinitroxides AMUPol or TEKPol, giving enhancements of the order of 200 at 9.4 T, dramatically loose efficiency at 18.8 T and suffer from a significant MAS dependence of their performances, with reduced sensitivity gains at fast MAS and depolarization effects in absence of microwaves. Here we show how a carefully design of the polarizing agent and the matrix formulation can significantly improve the DNP performances at high-field, fast MAS, and high temperature. Polarizing agents based on the Overhauser Effect like BDPA radical in OTP matrix, do not show any depolarization effects and the enhancement is indeed increasing with MAS over 100 at 18.8 T and 40 kHz MAS.1 In these conditions the enhancement is also persistent with temperature, reaching values around 30 just at –30 °C!3 As well, Cross-Effect polarizing agents with narrow-line radicals like hybrid BDPA-nitroxide biradicals show enhancements increasing with MAS frequency arriving up to 185 at 18.8 T and 40 kHz MAS, that are so far the best enhancement and sensitivity gain at high-field.2 We will present how the DNP performances of all these systems are explained by a combination of several factors, from the magnetic properties of the polarizing agent regulating the DNP mechanism to the role of the glassy matrix. Indeed, the spin-diffusion mechanism propagates the polarization in the whole sample, affecting the magnetization build-up time and the MAS dependence of the enhancement. Spin-diffusion is playing a crucial role in many the application: from pharmaceutical to material characterization, being often the key for a successful DNP ssNMR experiment.

Tuning Electronic Spin Properties of BDPA-Nitroxide Biradicals for Efficient Cross Effect DNP at Magnetic Fields up to 21.1 T

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Dynamic Nuclear Polarization (DNP) has been shown to be an important tool to overcome the sensitivity limitations of solid-state magic angle spinning (MAS) NMR, opening new possibilities and applications in the fields of materials and life sciences. Today, the most efficient polarizing agents are binitroxides such as AMUPol [1] or TEKPoI [2,3] featuring the Cross Effect as polarization transfer mechanism. However, the sensitivity gain from these binitroxide radicals has been shown to dramatically decrease with increasing magnetic fields [4-6]. Recently Mathies et al. introduced a new class of water-soluble biradicals, TEMtriPols, consisting of a hybrid between a broad EPR lineshape nitroxide moiety and a narrow EPR lineshape trityl radical [7].

Using a similar concept, we recently introduced a new series of hybrid biradicals employing nitroxides chemically tethered to BDPA (α,γ-bisdiphenylene-β-phenylallyl). The best radical in this series, HyTEK2, yields 1H enhancements of up to 185 at 18.8 T and 40 kHz MAS rate in a bulk frozen solution of 1,1,2,2-tetrachloroethane, which significantly outperforms current binitroxides. Here we will discuss the dependence of the DNP enhancement on the geometry of the linker and on the electron spin parameters (Tir, TM, electronic exchange coupling). We will report in particular EPR experiments to measure the exchange and dipolar couplings in this series of radicals.

Dynamic nuclear polarization (DNP) is used to enhance the signal intensity of nuclear magnetic resonance (NMR) spectroscopy by transferring spin polarization from free electrons to nuclei of interest.[1] Stable organic radicals such as nitroxides, as well as carbon-centered trityl- and 1,3-bisdiphenylene-2-phenylallyl (BDPA)- radicals, are commonly used as the source of free electrons for DNP.[2] The BDPA radical holds considerable potential as it has a narrow EPR line-width and is fairly easy to synthesize compared to trityl. However, BDPA radicals are not as stable as the nitroxides and trityl radicals. To our knowledge, no systematic study of the stability of BDPA radicals has been reported. Hence, we have synthesized various BDPA radicals and investigated their stability both in different solvents and in the solid state, using EPR spectroscopy. We have also optimized the reaction conditions (solvents, bases and oxidizing agents) used to generate the BDPA radical.

The chemical structure of bis-nitroxide polarizing agents critically determines the efficiency of cross-effect DNP. In particular, the interaction and relative orientation of the two nitroxide radicals should be optimal. Both parameters are affected by the molecular structure of the biradical in the frozen glassy matrix that is used in DNP/MAS NMR and likely differs from the structure observed with X-ray crystallography. We have determined the conformations of six bis-nitroxide polarizing agents, including the highly efficient AMUPol, in their DNP matrix with EPR spectroscopy at 9.7 GHz, 140 GHz, and 275 GHz. The multi-frequency approach in combination with an advanced fitting routine allows us to reliably extract the interaction and relative orientation of the nitroxide moieties. We compare the structures of the six bis-nitroxides to their DNP performance at 500 MHz/330 GHz.

Figure 1: Experimental (gray) and simulated (black) EPR spectra at (a) 9.706 GHz and (b) 139.997 GHz of PyPol (top) and AMUPol (bottom) in frozen d8-glycerol:D2O:H2O 60:30:10 v:v:v.
DNP-ENHANCED SSNMR SENSITIVITY: IMPROVED POLARIZING AGENTS FOR HIGH FIELDS


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Micro-wave driven dynamic nuclear polarization (DNP) is one of the most successful approaches to overcome the sensitivity limitations of solid-state NMR, opening new possibilities and applications in materials and life sciences. The recent advances result from significant developments in DNP instrumentation, in the introduction of new methodological concepts and in the design of ever more efficient polarization sources. In a DNP experiment, the larger polarization of unpaired electrons is transferred to surrounding nuclei by microwave irradiation at or close to the EPR Larmor frequency, providing maximum theoretical signal enhancements of a factor 658 for 1H and 2620 for 13C. The rational design of polarizing agents have contributed to the success of the technique at 9 T.[1,2] Signal enhancements ($\varepsilon$) of 50-200 are routinely obtained today at 9.4 T and 100 K, allowing the investigation (not feasible without DNP) of an ever broader range of molecular and macromolecular systems including biomolecules, hybrid materials, mesoporous silica, metal oxides, polymers, nanoparticles and microcrystals. However, the enhancement factors are still far from the predicted maximum values at high-fields (18 and 21 T). We will report our recent progress on the design, synthesis, EPR and ssNMR/DNP characterization of improved polarizing agents, giving large enhancement factors (ca. 180) at 18 T and 120K and opening new possibilities for structure determination.

We have recently investigated BDPA radical using a combination of MD simulations with spin dynamics simulations [1]. We have demonstrated that electron-nuclei hyperfine interactions are modulated by vibrations of BDPA radical, facilitating polarization transfer from electron to nuclei. Our findings are in agreement with experimental results [2] and offer an explanation why particular class of compounds shows Overhauser-DNP enhancement in insulating solids.

Now we focus on specific electronic and vibrational structures of BDPA that make it so distinct from other radicals, like Trityl. We use a combination of high level electronic structure calculations with DFT calculations to investigate vibronic coupling that leads to broken symmetry of the radical.

An efficient Gd$^{3+}$ based complex for high field Dynamic Nuclear Polarization

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High-spin gadolinium-based (Gd) metal complexes have been shown to act as polarizing agents (PAs) in magic-angle-spinning dynamic nuclear polarization (MAS-DNP) experiments$^{1-3}$. Gd$^{3+}$ is a half-integer spin characterized by a $m_s=1/2 \leftrightarrow -1/2$ central transition broadened by the zero-field splitting interaction. At moderate concentrations ($<20$ mM) the solid effect mechanism has been reported to induce $^1$H enhancement of about 10 for Gd-DOTA and smaller for GdCl$_3$ and Gd-DTPA$^3$ up to 9.4T.

Here we report the investigation of a Gd-based metal complex$^4$, Gd(tpatcn)$_3.3$H$_2$O, which offers an unprecedented $^1$H MAS-DNP signal enhancement at 9.4 T that we correlate to the particularly narrow $m_s=1/2 \leftrightarrow -1/2$ central transition and the corresponding long electron transverse relaxation time.

This observation offers a route to further optimize the complex design by improving the electron relaxation properties and corroborates the possibility to include high-spin metal systems as a viable alternative to more commonly used nitroxide mono- and biradicals spin probes. In addition, the compatibility of these complexes with physiological environments, as opposite to nitroxides, can broaden the scope of the presented research.

References:

In this contribution we present our first results with a low temperature MAS DNP NMR setup operating at 600 MHz / 395 GHz. The system consists of a Varian NMR system combined with a 395 GHz Bruker gyrotron that is coupled quasi-optically to a Tycko design Revolution 4 mm MAS DNP NMR probehead, allowing spinning of approximately 8 kHz at temperatures down to 25K. We will present details of the setup and show that, despite the fact that the system is still under development, the sensitivity obtained for natural abundant $^{13}$C spectra is very competitive in terms of sensitivity per unit time for polymeric materials.

As a first application we show a study of aramid finishes; polyaramid fibers have superior mechanical properties but are chemically almost inert. To incorporate these fibers into composite materials, such as tires, an activation finish is required for improved adhesion between the fibers and the rubbery-matrix of the composite material. The mechanism of this reinforcement is still under debate.

In order to study the finish and its interaction with the aramids by $^{13}$C and $^{15}$N NMR spectroscopy we need to overcome the challenges of the low concentration of the finish (1%-wt) in combination with the low natural abundance of the isotopes under study. Therefore, we selectively enhance the sensitivity at the interface by a DNP protocol by a matrix-free approach to incorporate stable DNP-biradicals into the finish material. We show that good DNP enhancements ($\varepsilon>60$) are obtained using this approach which allows us to selectively study the interface region of the composite polymer system. Based on the high sensitivity of this protocol ($^{13}$C SNR~4500 in a single scan), we explore which $^{13}$C-$^{13}$C DQ-SQ experiments are optimal for the moderate spinning speeds available under the conditions described above. We demonstrate that $^{13}$C-$^{13}$C correlation spectra are within reach for these challenging heterogeneous samples and discuss the implications of the chemistry we observe for the adhesion model in these composite materials.
263 GHz Klystron: A Lower-cost Route to Dynamic Nuclear Polarization

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Dynamic nuclear polarization (DNP) has revolutionized the study of materials by condensing NMR experiments that would previously have taken years into mere days or hours. Historically, micro- or millimeter-waves at the appropriate electronic frequencies for high-field DNP (263-593 GHz, to match NMR frequencies 400-900 MHz) have been generated by gyrotron sources in order to achieve sufficient irradiation power [1]. Gyrotrons, however, are large, expensive, and complex pieces of equipment with considerable facilities and footprint requirements. Recent advances in microwave source design have enabled solid-state DNP using lower-power klystron sources [2]. We present here the first commercial klystron-based DNP system at 400 MHz/263 GHz. Using a continuous wave klystron microwave source capable of output powers in excess of 5 Watts, we achieve large DNP enhancements in a very compact package, with unparalleled ease-of-use.

Further, we demonstrate a number of exciting applications of our klystron-based DNP system, ranging from pharmaceutical to materials science [3,4]. Despite its lower maximum output power, the klystron is able to virtually saturate the EPR absorption of common DNP biradicals even in the most challenging of samples. By providing enhancements as large as \( \varepsilon = 180 \), the klystron dramatically cuts down the acquisition time of challenging experiments. Even at natural isotopic abundance, 2-dimensional \(^{15}\text{N}-^{13}\text{C}\) correlations become possible in well under 10 hours with superb signal-to-noise, enabling structural characterization of complex materials in unprecedented detail.

Figure 1: Schematic of Klystron-based DNP Spectrometer. (b) Klystron DNP systems offer enhancements only slightly lower than those of their gyrotron-based counterparts, and are able to nearly saturate the electronic transitions of even dense radical-impregnated material samples (c).

In recent years, high-field Dynamic Nuclear Polarization (DNP), a technique capable of boosting the sensitivity of a NMR experiment by two to three orders of magnitude, has become an integral part of the NMR toolbox. Currently, solid-state DNP-NMR (ssNMR) experiments are performed at magnetic field strengths corresponding to \(^1\)H NMR frequencies up to 900 MHz. As a result, DNP enables scientists to conduct experiments that were unthinkable even a decade ago.

DNP-enhanced ssNMR experiments are typically performed at temperatures well below 100 K and to efficiently saturate the corresponding EPR transitions, several watts of high-power, high-frequency THz radiation are required. At frequencies of 263 GHz (400 MHz \(^1\)H, 9.4 T) and higher, the gyrotron is the only demonstrated device capable of generating sufficient output power over a long period of time. Since the gyrotron requires an additional, superconducting magnet with a magnetic field strength slightly higher than the corresponding NMR experiments, the device is typically operated as a second harmonic device. This effectively reduces the required magnetic field to approximately half the value required for the NMR experiment. However, a second harmonic gyrotron is more challenging to design and has limited frequency tuning but is accepted as a solution to reduce the overall system cost.

Here we present stable operation of an integrated THz system for DNP NMR spectroscopy operating at an output frequency of 263 GHz. This novel fundamental mode gyrotron does not require an additional superconducting magnet and is designed to operate inside the bore of the NMR magnet, just above the NMR probe. It currently produces several watts of output power, shows extremely high frequency stability and a frequency tuning of > 200 MHz. We will review the operational characteristics of the gyrotron tube and demonstrate first DNP results under MAS conditions.
# Participants

*In the case of posters, only the presenter is listed*

ASTA = Ampère Student Travel Award  
ISTA = ISMAR Student Travel Award

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