

## Physico-chemical Principles of Hyperpolarized Contrast Agents

Walter Köckenberger

Sir Peter Mansfield Magnetic Resonance Centre, School of Physics and Astronomy, University of Nottingham, Nottingham NG7 2RD, United Kingdom

Email: *walter.koekenberger@nottingham.ac.uk*

### Spin polarization

The concept of thermal and non-thermal polarization of a spin ensemble is discussed and the role of spin polarization for the sensitivity of magnetic resonance experiments is analyzed. There are a number of strategies that can be used to generate molecules carrying nuclei with very high degree of spin polarisation. These strategies are described in detail and the underlying spin physics is explained. Furthermore, technical requirements for implementing these strategies are summarised and instrumental challenges outlined that need to be overcome when optimising these strategies.

Strategies covered in this course are optical pumping, parahydrogen-induced polarization and dynamic nuclear polarization.

### Optical Pumping

Optical Pumping (1) can be used to generate highly polarised noble gases for magnetic resonance imaging applications. In particular, helium-3 (2), xenon-129 (3) or krypton-83 (4) can be prepared with high nuclear spin polarization that is enhanced by several orders of magnitude in comparison to thermal polarization. In optical pumping angular momentum from laser light is transferred to electronic and nuclear spins. There are two different technical implementations. Metastability Exchange Optical Pumping (MEOP) can be used to generate specifically high helium-3 polarization. Spin Exchange Optical Pumping (SEOP) has a more general applicability. The main difference between these two techniques is the initial step in which the laser photons interact with the noble gas atoms. In the case of SEOP electrons in alkali-metal vapour are first polarised using circular polarised light and the polarisation is then transferred via collisions between the metal atoms and the noble gas. In MEOP electrons in helium-3 atoms are excited and polarization is distributed via collisions between the helium atoms.

### Parahydrogen Induced Polarization

Parahydrogen induced polarization (PHIP) (5) and its variant SABRE (Signal Amplification By Reversible Exchange) (6) rely on the use of diatomic hydrogen gas in the para rotational state. In the original version hydrogen nuclei are transferred in pairs onto substrate molecules in a hydrogenation reaction. Since the rotational state of the molecules is correlated with a particular spin state a high level of polarisation can be generated on the product molecules. SABRE overcomes the requirement of a pairwise hydrogen transfer onto the target molecules for the generation of polarisation. Instead the diatomic hydrogen molecule is bound to a catalyst which itself associates temporarily with the target molecules. The hydrogen spin polarisation is then transferred via scalar couplings to the target molecules. While the original PHIP experiment is restricted to substrate molecules with unsaturated bonds, SABRE makes it possible to polarise a wider range of molecules. A successful application of PHIP requires insight in the spin dynamics of the target molecules since anti-phase coherence arises initially from the hydrogenation reaction. For optimal signal detection the experimental condition must be carefully chosen.

### Dynamic Nuclear Polarization

A third approach, known as dynamic nuclear polarisation (DNP) which was already described in 1958 by Abragam et al. (7), can significantly enhance nuclear polarisation by transferring the large electron polarisation to the nuclear spin system. The DNP enhancement is proportional to the ratio of the electron and nuclear gyromagnetic factors which is ~660 for  $^1\text{H}$  nuclei but this factor is experimentally never fully obtained. The polarisation transfer is driven by microwave irradiation at or near the electron Larmor frequency. The overall DNP enhancement depends on the details of the polarisation transfer pathways and the properties of the participating molecules. The DNP mechanisms include the Overhauser effect (8) that plays a role in liquid state applications and several pathways active in solid samples. A limiting factor in liquid state application of DNP is the high dielectric constant of water that prevents the penetration of high frequency microwaves into the sample and that leads to sample heating. An important contribution in this respect was made by Goldman et al. who demonstrated that in glassy samples the nuclear spin polarisation could be

enhanced by DNP at cryogenic temperatures (~1.5K) and modest magnetic fields (3.4T) in a 'stand-alone-polarizer'. Subsequently the samples can be dissolved in a small volume of hot water to produce a solution containing molecules with high non-thermal nuclear spin polarisation (9). This strategy, termed dissolution DNP, can generate a signal enhancement of three to four orders of magnitude in comparison to the signal acquired at ambient temperature. The maximal enhancement that can be achieved in such experiments shows a complex dependence on radical properties and sample composition as well as external factors such as static and mw magnetic field strength.

---

<sup>1</sup> Happer W. 1972 *Rev. Mod. Phys.* **44**(2) 169–249.

<sup>2</sup> Middleton et al, *Magn. Res. Med* **33** 271–275.

<sup>3</sup> Albert et al 1994 *Nature* **370**, 199 – 201.

<sup>4</sup> Pavlovskaya et al, *Proc Natl. Acad. Sci. USA* **102**(51), 18275-18279.

<sup>5</sup> Bowers CR & Weitekamp 186 DP, *Phys Rev Lett.* **57**(21), 2645-2648.

<sup>6</sup> Duckett et. al. 2009 *Science*, **323**(5922), 1708 – 1711.

<sup>7</sup> Abragam et al 1958, *C R Acad Sci* **247**, 1852.

<sup>8</sup> Overhauser 1953, *Phys Rev* **92**, 411.

<sup>9</sup> Ardenkjaer-Larson et al. 2003, *Proc. Natl. Acad. Sci. USA*, **100**(18) 10158.