Imaging Metabolism with Hyperpolarized Nuclei

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Methods for Hyperpolarizing Nuclear Spins

- There are several very different methods for hyperpolarizing nuclear spins
- Hyperpolarization enhances the MR signal more than 100,000-fold
- The hyperpolarization decays irreversible on the order of minutes
- Hyperpolarization has been used clinically

This lecture aims at basic scientists and clinicians, who want to understand the physics, instrumentation and methodology of hyperpolarizing nuclear spins. The course is focusing on imaging of metabolism with hyperpolarized nuclei, and currently only one hyperpolarization method is generally capable of hyperpolarizing biological molecules in solution: the dissolution-DNP method [1]. The focus will therefore be on this method. At the end of this lecture the audience should be able to judge opportunities and limitations of the hyperpolarization method, as well as the skills and infrastructure required to successfully apply hyperpolarization to metabolic imaging studies.

The lecture briefly describes the different methods of hyperpolarizing nuclear spins in solution, in particular para-hydrogen induced polarization (PHIP) and dissolution Dynamic Nuclear Polarization (dissolution-DNP). Optical pumping methods are only capable of hyperpolarizing ^{3}He and ^{129}Xe in the gas phase, and therefore has little role in metabolic imaging. The dissolution-DNP method is further elaborated.

At a magnetic field strength of 3 T and room temperature the nuclear spin polarization of ^{13}C is only 2.5 ppm. In addition the sensitivity of ^{13}C is further reduced by the low natural abundance (1.1 %). By enrichment of ^{13}C and hyperpolarization, enough signal is available to follow the metabolic fate of the biomolecule. Selective enrichment of carbon positions with long T1 maximizes the life time of the hyperpolarization.

Dissolution-DNP takes advantage of DNP in the solid state followed by rapid dissolution in a suitable solvent [2]. The polarization is retained in the dissolution creating a solution with a non-thermal nuclear polarization approaching unity. DNP requires the presence of unpaired electrons, which are added to the sample as, e.g., an organic free radical. In order for the DNP process to be effective, the radical must be homogeneously distributed within the sample. To achieve this, glass-formers, e.g. glycerol or DMSO, can be added to prevent crystallization and produce an amorphous solid when cooling the sample. The high electron spin polarization at low temperature is then transferred to the nuclear spins by microwave irradiation. The physics of DNP is quite complicated and several mechanisms can be effective. The physics will be explained in simple terms. Following the solid state polarization the sample is dissolved in a buffer. The buffer is heated to an elevated temperature (100-200 °C) and injected onto the sample at high flow rate to efficiently melt and dissolve the solid sample.

Common to all hyperpolarization methods is that the decay of the hyperpolarized spins to thermal equilibrium limits the time window available for the experiment. For molecules in solution the nuclear longitudinal relaxation time is typically 30-60 seconds in vivo for carbonyls or carboxylic acids in small molecules. In special cases, and for some other nuclei, it can be longer. Noble gases in the gas phase can have much longer relaxation time allowing storage and transportation over longer distances. The understanding of relaxation processes for nuclear spins is an important aspect of hyperpolarization at all stages of the process. The phase transitions that occur in the process and the large range of temperature and magnetic field conditions mean that a fundamental understanding of relaxation mechanisms is essential.

The instrumentation involved in these hyperpolarization techniques varies widely due to the nature of the physical mechanism. This has consequences for the strategy chosen in terms of integrating the polarization method with the MR experiment. The short life time of the nuclear polarization makes the logistics of hyperpolarization demanding. The instrumentation is briefly introduced and described.

[1] J. Kurhanewicz, D. B. Vigneron, K. Brindle, E. Y. Chekmenev, A. Comment, C. H. Cunningham, R. J. DeBerardinis, G. G. Green, M. O. Leach, S. S. Rajan, R. R. Rizi, B. D. Ross, W. S. Warren, and C. R. Malloy, "Analysis of Cancer Metabolism by Imaging Hyperpolarized Nuclei: Prospects for Translation to Clinical Research," *Neoplasia*, vol. 13, no. 2, pp. 81–97, Feb. 2011.

[2] R. E. Hurd, Y.-F. Yen, A. Chen, and J. H. Ardenkjaer-Larsen, "Hyperpolarized 13C metabolic imaging using dissolution dynamic nuclear polarization," *Journal of Magnetic Resonance Imaging*, vol. 36, no. 6, pp. 1314–1328, 2012.