REPRODUCIBILITY AND QUALITY ASSURANCE IN HYPERPOLARIZED 13C MRI AND MRS

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Introduction Recent improvements in **d**ynamic **n**uclear **p**olarization (DNP) and **P**arahydrogen **a**nd **s**ynthesis **a**llow **d**ramatically **e**nhanced **n**uclear **a**lignment (PASADENA) provide signal enhancement in excess of 10^5 fold for ^{13}C MRI *in vitro* and *in vivo*. This has allowed sub-second angiography (Golman, *et al*, MRM 2001), ^{13}C chemical shift imaging (CSI) of *in vivo* heart and lung (Bhattacharya *et al*, ISMRM 2005), true metabolic imaging and spectroscopy of normal tissues and implanted tumors (Checkmenev *et al*, SMI 2006). The major challenge for biological studies with hyperpolarized molecules is the relatively short – usually less than 1 minute – relaxation time T_1 and poorly defined survival of ^{13}C signal during and after parenteral administration *in vivo*. It is therefore not surprising that a noteworthy omission from all published studies to date with hyperpolarized carbon is evidence of reproducibility. Here, we present recently developed methods of quality assurance (QA) leading to unprecedented levels and reproducibility of PASADENA hyperpolarization.

Aim Define and optimize the crucial factors limiting reproducibility and yield of hyperpolarization during *in vitro* and *in vivo* PASADENA ^{13}C MRI and MRS.

Instrumentation Mark I Malmo parahydrogen generator with iron oxide catalyst at T=20K was continuously supplied with pure hydrogen (Praxair) producing 97.9±0.9% quality para-H_2 (>25 batches tested). Mark I parahydrogen reactor/polarizer for low-field PASADENA, designed by Dr. Oskar Axelsson (Nycomed, Amersham Bioscience, London) and constructed at Promech (Malmo, Sweden) was located at distinct positions to each MR instrument: (i) high resolution vertical bore Varian Mercury 7T NMR spectrometer, (ii) horizontal bore Bruker Avance 4.7T animal scanner, and (iii) 1.5T GE Signa clinical scanner, all equipped with ^{13}C detection capability. 1-^{13}C-hydroxyethyl acrylate (HEA) (Sigma-Aldrich; Miamisburg, Ohio) dissolved in aqueous solution along with norbornadiene rhodium catalyst is sprayed in the polarizer reservoir (200 mL polysulfone reactor) filled with 10 bar para-H_2, where parahydrogen molecule reacts with precursor molecule and the polarization transferred from ^{1}H nuclei of p-H_2 to target ^{13}C nucleus. 3ml of hyperpolarized product was withdrawn after t=4.2 seconds allowed for RF polarization transfer and chemical reaction.

Results **Chemistry:** While many factors govern reproducibility of PASADENA including sophisticated chemistry, we find that all chemical ingredients: labeled reagents, organic ligand, metal catalyst, are produced by industry suppliers with high quality. The "weakest links" limiting reproducibility related to polarization transfer from ^{1}H to ^{13}C spins are RF pulses or B_1 and homogeneous and stable B_0, where chemistry and polarization transfer are accomplished. The calibration of these two variables with reproducible para-H_2 production on site, allow us to achieve remarkable reproducibility of high levels of ^{13}C polarization using commercially available chemicals.

NMR Calibration: The width for the RF pulse effecting optimal spin inversion was determined for ^{13}C, $t_{180°}$ = 200 µs, and for ^{1}H, $t_{180°}$ = 210 µs, at constant amplitude, 25 V peak-to-peak voltages, by variation of the excitation pulse width in the polarizer and detection in 7T Varian spectrometer, Figure 1. To determine the optimal static field B_0, a thermally polarized sample was employed to the effect of the optimized 180° square pulse inside of the polarizer, followed by detection of NMR signal at 7T. The optimal static field B_0 was at [+1.73 ±0.02] mT with steep signal drop off outside this range (Fig. 2). As expected, the maximum hyperpolarization was found within this range at +1.725 mT in successive experiments. Employing the optimized B_0 and B_1 field and the same chemistry conditions, we obtain highly reproducible hyperpolarization with maximal variation of STD=3.1% in successive experiments (PASADENA permits repeated experimentation every 2 – 5 minutes, Table 1). The absolute value of achieved polarization, however, varied on successive days.

Discussion Excellent reproducibility of hyperpolarization (±2.8% HP) was achieved within consecutive intervals of 2 – 5 minutes. The maximum of achieved polarization was 23.5% (101,000 fold enhancement), with considerable variation on successive days. We recommend these minimal QA process before each run of PASADENA studies.

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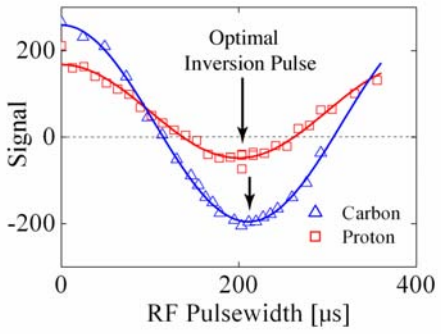

Fig. 1. Calibration of the RF pulse width for ^{13}C and ^{1}H channels of PASADENA polarizer at 25 Vpp. Inversion was performed in the reactor at 1.725mT and detection in 7 T Varian spectrometer.

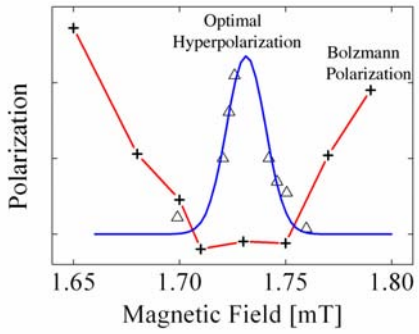

Fig. 2. Optimization of static field B_0 using Boltzmann polarization at 7T (inversion recovery experiment, red line, crosses) and hyperpolarized sample (blue line, triangles).

#	P [%]	±STD	N	Enhancement
1	9.4	±0.5	3	23,000 fold
2	20.6	±2.8	4	50,000 fold
3	23.5	±2.2	2	101,000 fold
4	6.5	±1.6	4	10,000 fold
5	11.0	±5.2	8	15,000 fold
6	9.0	±7.4	8	18,000 fold

Table 1. Six experiments to determine the stability of PASADENA hyperpolarization. B_0 was varied in experiments 5, 6. Detected on 4.7T Bruker animal scanner (1, 2), 1.5 T GE Signa clinical scanner (3) and 7T Varian high resolution spectrometer (4-6). P: Polarization, STD: Standard deviation, N: Number of experiments.