PASADENA hyperpolarization: Instrumentation and preparation of tracers for in vivo application

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Motivation In the dawn of hyperpolarization (HP) of molecules in solution for biomedical application, the question of suitable instrumentation is imperative. Dynamic Nuclear Polarization (DNP) polarizers are commercially available, but rather cost-intensive. Nevertheless, DNP is used by an increasing number of laboratories, while Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment (PASADENA) [1, 2] is presently installed only in very few places (<5). This may be attributed to the fact that only few molecules and no instrumentation for PASADENA of biomolecules are commercially available or published in scientific literature. Here, we present a polarizer for the reliable hyperpolarization of a variety of molecules, including novel biomolecule 1-^{13}C, 2,3-D_2 Succinate [7] and other molecular agents.

Materials A new polarizer for the reproducible hyperpolarization of isotopically-labeled biomolecules by PASADENA in solution suitable for small animal research was designed (Fig. 1) [6]. NMR signal enhancement and HP yield was quantified in respect to a thermally polarized sample. The preparation of parahydrogen and chemistry is described elsewhere [5]. In each experiment, a volume of (3.0 ± 0.5) ml was produced within minutes. Spin order transfer by Goldman and Johannesson [3] was employed. A combination of three free-evolution periods (t_1, t_2, t_3) and three pulses (p_1, p_2, p_3) is utilized after the decoupling and hydrogenation reaction. The free-evolution intervals t_1, t_2, t_3 depend on the J-couplings of the molecules employed and were calculated according to [3] with theoretical maximum Polarization P > 0.99.

Fig. 1: The PASADENA polarizer.

Results Reproducibility and hyperpolarization yield of 1-^{13}C, 2,3-D_2 succinate using the new apparatus was investigated in series of experiments on different days: $P_{hyp}^{t=33}$ = (0.064 ± 0.02) was detected t = (33 ± 0.5) s after sample preparation. By measuring ^{13}C T_1 = (39.6 ± 0.6) s in D_2O at pH = 3 the nascent level was estimated to $P_{hyp}^{t=0} \approx 15$ %. Similar levels of hyperpolarization for other molecules were readily achieved. After injection into a rat, ^{13}C MRI of (5 mm)^3 resolution image was obtained in 0.3 s per slice. ^{13}C MRS showed strong signal enhancement.

Conclusion The new automated equipment requires only one person to operate and allows producing hyperpolarized samples of 1 - 5 ml every three minutes with high reproducibility suitable for biomedical *in vivo* research.

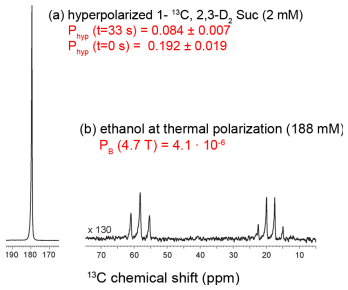

Fig. 2: ^{13}C hyperpolarization of 1-^{13}C, 2,3-D_2 Succinate.

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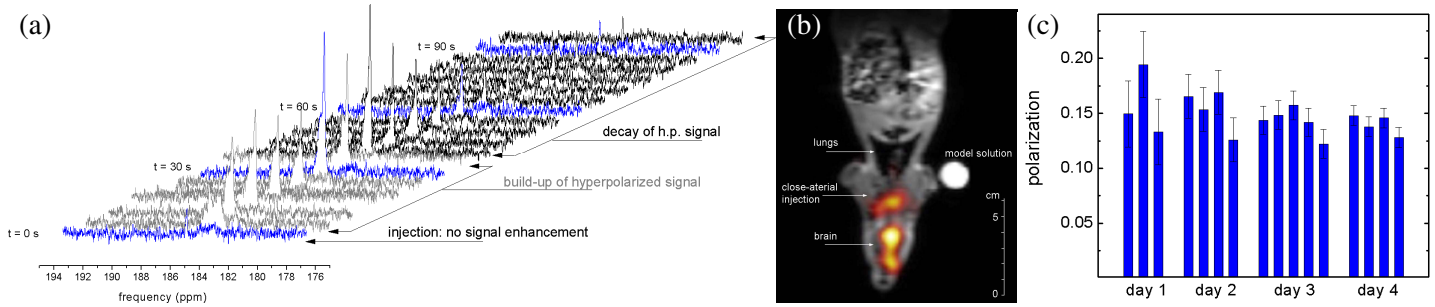

Fig. 3: (a) unlocalized serial *in vivo* ^{13}C-NMR spectroscopy of a rat head after injection of hyperpolarized succinate in the carotid artery with NEX = 1, TR = 5 s, and 15 Hz line broadening, (b) Subsecond coronal *in vivo* ^{13}C and ^{1}H MRI after close arterial injection of hyperpolarized succinate (1 ml, 25 mM) in a rat, overlaid over anatomical ^{1}H MRI. ^{13}C MRI sequence was 3D FIESTA with TR = 6.3 ms, and TE = 3.1 ms, measurement time = 0.3 s per slice, (5 mm)^3 spatial resolution, FOV = 220 mm / 320 mm, 44 phase encoding steps / 64 readout points, (c) reproducibility of ^{13}C hyperpolarization of 1-^{13}C, 2,3-D_2 Succinate.