A flexible multi-sample DNP system for rapid sequential dissolutions

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Introduction: Dissolution Dynamic Nuclear Polarization (DNP) has gained considerable momentum in both oncology (1) and cardiovascular applications (2). For various procedures, consecutive injections are required to study transient metabolic changes during pharmacological or structural interventions. Accordingly hyperpolarized samples need to be available in rapid succession. Given the polarization build-up time of 1 hour and more, system designs need to accommodate multiple samples to be polarized simultaneously.
A number of single sample DNP systems have been presented over recent years (3-6). Besides a report of a dedicated sterile system capable of polarizing up to four samples (7), there have also been recent efforts utilizing standard wide-bore magnets including a revolver based system accommodating up to six samples (8).
In order to facilitate construction and operation of such a system, a greatly simplified design is introduced here permitting polarization of up to four samples for rapid sequential dissolution with less than 10 min latency in-between. Basic design criteria and performance measurements are presented.

Methods: The insert DNP system is designed to be operated in conjunction with a standard wide-bore vertical magnet charged to 3.35 T (Bruker Biospin, Switzerland), a Spectrostat NMR cryostat (Oxford Instruments, UK) and a commercially available 94 GHz microwave source (Elva Microwave, Russia). The general design of the system is shown in Figure 1. The top plate, which is mounted at the cryostat end, feeds the microwave WR28 waveguide and up to four identical sample sticks. Each sample stick is composed of two functional elements: a dissolver, locked into the skeleton port and a lifter moving ca. 5cm within a dissolver. The lifter is inside the dissolver except for the upper end being a pulling rod exposed at the top of the stick and the lower end containing a sample holder (Figure 1 right). Microwaves are irradiated onto all samples simultaneously without any dedicated cavity being used.
Pilot experiments were conducted using samples of a 25.4 µl mixture of [1-13C] labeled pyruvic acid and 13.5 mM trityl radical doped with 1.5 mM Dotarem (Guerbert, France) at a temperature of 1.4 K for about 130 minutes using a microwave source setting of 120mW. After the hyperpolarization process the samples were dissolved with 8 ml Tris buffer, resulting in a pyruvate concentration of about 40 mM. After the dissolution process the sample was transported to a 9.4 T small animal MR system. Two successive dissolution experiments within a 10 min period were conducted for initial performance testing. To test the influence of dissolution on cryostat temperature, two consecutive dissolution attempts were carried out on the same stick.

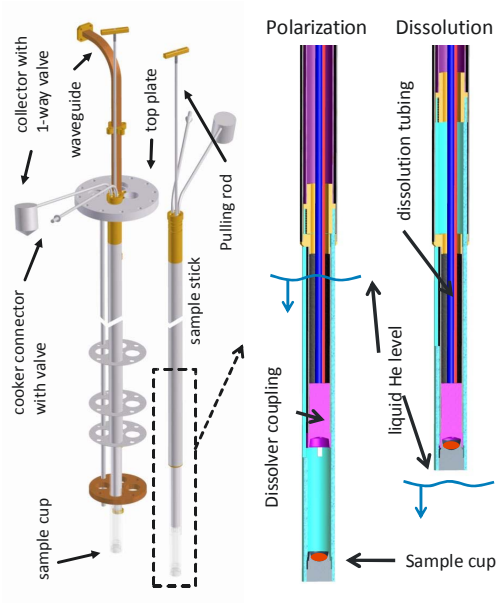

Figure 1: Polarizer skeleton with one sample stick mounted and a free stick (left). The bottom part indicated by the dashed box is shown on the right during polarization and dissolution. The sample is marked in red.

Results: The system was successfully assembled and temperature of 1.4 K reached. Liquid-state polarization extrapolated to the beginning of the dissolution was found to be 19.2 and 18.2 % for the first and second sample, respectively (Figure 2). The solid-state signal build-up and the cryostat temperature as recorded prior and during two successive dissolution experiments are shown in Figure 3. Solid-state polarization of the observed sample decreased by 7% after dissolution of the second sample. The helium bath temperature increased briefly from 1.4 to 1.9 K during the dissolution process but stabilized quickly (Figure 3, bottom row).
Discussion: In this work a simple multi-sample dissolution DNP insert has been presented permitting dissolution of multiple samples within a 10 min period. The design is scalable as each sample stick is constructed in an identical manner. Operation of the system is facilitated by the fact that all components remain in the cryostat under vacuum and interchange of microwave and dissolution paths as required with other systems is not necessary. Compared to the multi-sample system published elsewhere (7) the dissolution volume could be restricted to 8 ml hence minimizing dead volumes during prospective in-vivo experiments in small animals.

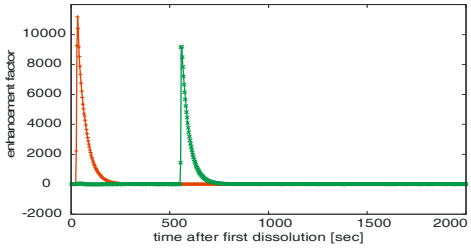

Figure 2: Enhancement factors of 23100 and 22000 (extrapolated) in the liquid state just upon dissolution of the first (red) and second samples (green) were achieved. The time lapse between first and second dissolution was 9 min. Spectra were recorded in a 9.4T magnet ca. 35s after dissolution.

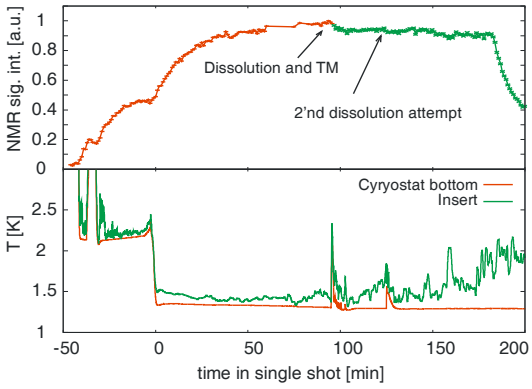

Figure 3: Solid-state NMR signal demonstrating effects of dissolution performed in the second stick (upper plot) together with a temperature record (lower plot).

References: (1) Kurhanewicz J et al. Neoplasia 2011; (2) Schroeder MA et al. Circulation 2011; (3) Ardenkjaer-Larsen JH et al. PNAS 2003; (4) Comment A et al. Conc Magn Reson 2007; (5) HyperSense, Oxford Instruments; (6) Granwehr J et al. J Magn Reson 2007; (7) Ardenkjaer-Larsen JH et al. NMR in Biomed 2011; (8) Batel M et al. J Magn Reson 2012.