Characterization of Solid State Dynamic Nuclear Polarization for Metabolic Imaging

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Introduction

Whilst MRI is widely used in healthcare to assess tissue structure and function, the application of MR for metabolic imaging has been limited by intrinsically low sensitivity. In proton MRI, low sensitivity is compensated for by a high proton concentration in samples; unfortunately this is not true for low natural abundance magnetic nuclei such as ^{13}C. Dynamic nuclear polarization (DNP) is an established method that can achieve virtually 100% polarization levels in solid-state, paramagnetic samples (1, 2). Recently, Ardenkjær-Larsen *et al* (3) utilized DNP in a novel method, DNP-MR, to obtain highly polarized nuclear spins in solution. DNP-MR consists of DNP of ^{13}C nuclei followed by rapid dissolution, resulting in liquid state polarization in excess of 20% (3). As a result, dynamic, *in vivo* visualization of a given metabolite, and its conversion to other species, has become a possibility. This study was carried out to characterize the DNP process specific to the application of DNP-MR, and to optimize solid state polarization with a view to maximizing liquid state polarization. All equipment associated with sample polarization, in a hyperpolarizer designed specifically for DNP-MR, has been previously described (3).

Methods

A 40 mg aliquot of 99% enriched 1-^{13}C-pyruvic acid, doped with 15 mM of trityl radical (3), was placed in the hyperpolarizer. To determine the optimal frequency for polarization, the microwave frequency was increased from 93.840 GHz to 93.940 GHz, in 2 MHz steps, at a power of 33.1 mW. Polarization at each frequency step was measured after 600 s of build-up, with a 110 µs pulse. At the frequency for positive polarization enhancement, aliquots of 1-^{13}C-pyruvic acid were polarized for 9000 s and the polarization was monitored with very low flip angle RF pulses (TR = 300 s). The experiment was repeated with sample sizes of 30, 40 and 50 mg, and at 14 logarithmically-spaced values of microwave power, spanning the output range of the microwave source. Hyperpolarizer function was carefully monitored to ensure the sample was located in a bath of liquid helium at 1.12 ± 0.08K. Solid-state polarization build-up data were modelled as a first-order exponential function and the polarization time constant was calculated for each build-up curve. To further investigate the effect of incident microwave power on polarization, the original frequency sweep experiment was repeated at incident powers of 0.2, 2.7, 33.1 and 148.4 mW.

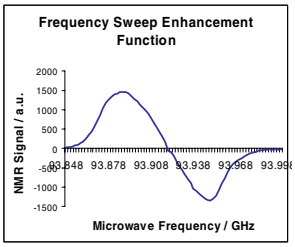

Figure 1 *Frequency sweep at 33.1 mW.*

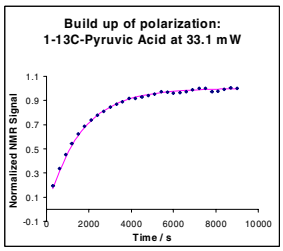

Figure 2 *Example polarization build-up curve at 33.1 mW.*

Results

Figure 1 shows the polarization enhancement as a function of microwave frequency for an incident power of 33.1 mW. The optimal positive and negative enhancement frequencies were determined to be 93.910 GHz and 93.950 GHz respectively. The enhancement function demonstrated an asymmetric pattern, possibly due to asymmetry in the radical electron paramagnetic resonance (EPR) spectrum (4). Figure 2 demonstrates an example polarization build up curve for a 30 mg sample, along with its respective first-order exponential fit.

Figure 3a depicts the relationship between incident microwave power and build-up time constant for a range of sample masses. Increasing microwave power leads to an increase in the rate of polarization enhancement. Figure 3b demonstrates a similar relationship between steady-state signal magnitude and microwave power for the lower power levels (< 33.1 mW). However, at higher microwave power levels (> 33.1 mW) the relationship was reversed. Based on gradient information, large samples seemed to intensify the relationship between steady-state signal amplitude and microwave power.

Figure 4 demonstrates the effect of increasing microwave power on the frequency sweep enhancement function. At higher microwave powers the enhancement peaks broaden and the optimal frequency of enhancement shifts away from the function's centre.

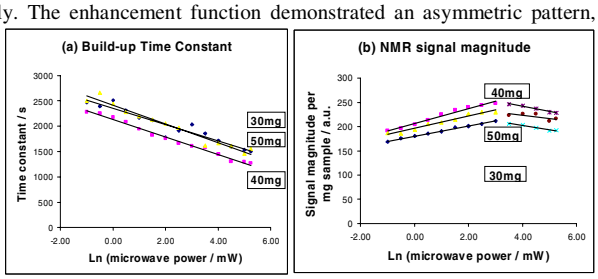

Figure 3 *The effect of sample mass and microwave power on (a) polarization time constant and (b) signal magnitude.*

Discussion and Conclusions

The shift of the positive enhancement peak to lower frequencies with increasing microwave power provides an indication of a change in the underlying DNP process (5). At 148.4 mW, the enhancement peaks display a 71 MHz separation, approximately twice the nuclear Larmor frequency, as would be expected if the solid effect had a significant role in DNP enhancement. However, at powers below 33.1 mW the enhancement peaks were separated by < 60 MHz, indicating that at low incident power thermal mixing is the dominant mechanism of DNP. The variation in the shape of the enhancement function at different microwave powers explains the relationship seen between steady-state signal magnitude and incident power (Figure 3b). The maximal steady-state signal magnitude was achieved at 33.1 mW because the microwave frequency was set to the optimum enhancement frequency for that power level; for other microwave powers a decreased steady-state signal magnitude was observed because the applied frequency had not been optimized.

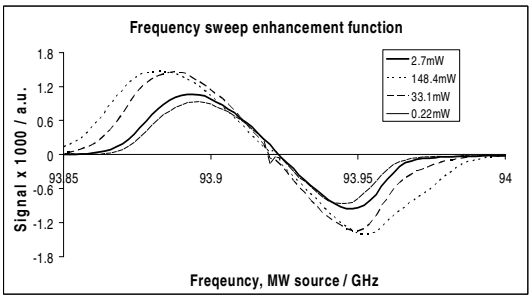

Figure 4 *Frequency sweep experiments at 0.2, 2.7, 33.1, 148.4 mW.*

When performing *in vivo* metabolic imaging experiments, it is essential that contrast agent polarization levels are sufficiently high for the visualization of both the contrast agent and its lower concentration metabolic products. Interconnected, user-controlled hyperpolarizer parameters, such as microwave power and frequency, affect solid state polarization enhancement rates and levels. Future work will investigate sample size to fully characterize the relationships explored in this study. Also, frequency sweeps allowing 2 hr of build-up at each point will be performed to determine the dependance of polarization time upon incident microwave frequency. These studies will help to quantify the relative contributions of thermal mixing and the solid effect to the DNP mechanism characteristic of DNP-MR, and will provide a true set of optimized system parameters.

References: (1)Jeffries. Phys Rev. 106, 164-165 (1957), (2) de Boer and Niinikoski Nucl Inst Meth. 114, 495-498 (1974), (3)Ardenkjaer-Larsen et al. Proc Natl Acad Sci USA. 100, 10158-63 (2003), (4) Wolber at al. Nucl Inst Meth Phys A 526, 173-181 (2004). (5)Wind et al. Prog NMR Spec. 17, 33-67 (1985).