Thermal T_1 measurements for frequently used ^{13}C hyperpolarization agents at clinically available field strengths

Stephan Düwel[1,2], Patrick Christ[1,3], Ulrich Köllisch[1,3], Markus Durst[1,3], Concetta V Gringeri[3,4], Franz Schilling[4], Marion I Menzel[3], Rolf F Schulte[3], Steffen Glaser[2], Markus Schwaiger[4], and Axel Haase[1]

[1]*Institute of Medical Engineering, Technische Universität München, Garching, Germany,* [2]*Department of Chemistry, Technische Universität München, Garching, Germany,* [3]*GE Global Research, Garching, Germany,* [4]*Institute of Nuclear Medicine, Klinikum Rechts der Isar, Munich, Germany*

Introduction: Hyperpolarized ^{13}C metabolic MR spectroscopic imaging of pyruvate and its down-stream metabolites alanine and lactate allows real-time in-vivo studies of energy metabolism in healthy and tumor tissue [1]. At the same time, tumor perfusion can be studied using metabolically inactive hyperpolarized agents such as urea [2], whereas hyperpolarized acetate can be used to examine short chain fatty acid metabolism in vivo [3]. Research facilities and clinics perform spectroscopic magnetic resonance imaging (MRSI) experiments at increasingly higher magnetic field strengths B_0 (1T, 3T, 7T, 14T) because of availability, higher spectral resolution and better thermal signal to noise ratio (SNR). Recently, it was shown that hyperpolarized experiments at even lower fields can theoretically be more sensitive than high-field MRI [4]. Long longitudinal relaxation times (T_1) could favor experiments at low magnetic field strengths even further. In this study, we systematically measured T_1 times for the aforementioned ^{13}C hyperpolarization agents at clinically available field strengths (1.05T, 3.0T, 7.0T) and 14.1T under constant conditions (pH, temperature, concentration), facilitating a proper design of time critical hyperpolarization experiments at varying field strengths.

Methods: All labeled compounds ([1-^{13}C]pyruvate, [1-^{13}C]alanine, [^{13}C]urea, [1-^{13}C]acetate, [1-^{13}C]lactate) and TRIS buffer were dissolved 1:1 (c/c) in distilled water, each compound at a concentration less than half of their maximum solubility. All solutions were neutralized and titrated with NaOH or HCl into the physiological pH value around 7.4. All experiments were conducted at room temperature. On all systems, an inversion recovery (IR) sequence was set up with equally spaced inversion times (TI), one excitation per TI and covering a range from 0s to 5xT_1. The repetition time (TR) was set to five times the expected T_1 or longer. The signal equation

$$S(TI) = S_0|1 - (1 - cos \propto)exp(-TI/T_1)| \quad (1)$$

was used to estimate the equilibrium magnetization S_0, the flip angle α and the longitudinal relaxation time T_1 from a three-parameter non-linear least squares fit. **1T:** Experiments at 1.05T were performed with custom made 3.5mL spherical phantoms in a ^{1}H-^{13}C dual tuned mouse coil on an Aspect M2 permanent magnet small animal scanner (Aspect Magnet Technologies, Netanya, Israel), where a standard inversion recovery (IR) sequence was implemented in NTNMR (Tecmag, Houston, USA). Prior to each ^{13}C scan, a 90° pulse proton navigator scan was performed to determine the actual proton resonance frequency and calculate the corresponding ^{13}C frequency to be used in the upcoming ^{13}C scan. Low SNR data were line broadened and peak maxima were corrected according to the Rice distribution [5]. Matlab (MathWorks, Natick, USA) was used both for real-time control of the scanner via a software interface to NTNMR and for post-processing. **3T:** Experiments at 3.0T were performed with 3.5mL spherical phantoms in a ^{13}C home-built solenoid coil in a Discovery MR750w (GE Healthcare, Milwaukee, USA), where a standard IR sequence was implemented. **7T:** Experiments at 7.0T were performed with 3.5mL spherical phantoms on a ^{13}C two channel flexible array surface coil in a Discovery MR901 small animal scanner (Agilent Technologies, Santa Clara, USA and GE Healthcare, Milwaukee, USA), where a standard IR sequence was implemented. **14T:** Experiments at 14.1T were conducted in a dual tuned coil with a D_2O glass capillary added to a standard 5mm 600µL NMR tube on an Avance600 NMR spectrometer (Bruker BioSpin, Rheinstetten, Germany) using an available T_1 IR sequence with higher order shimming and frequency locking to D_2O.

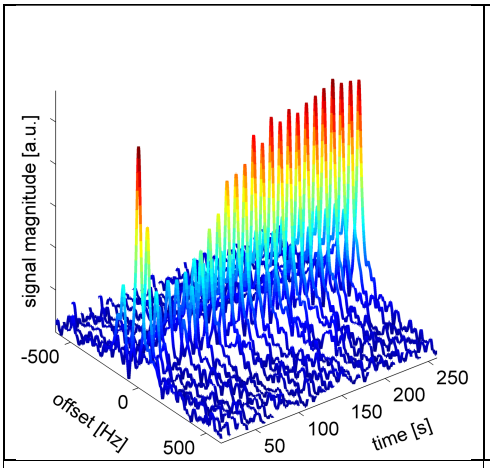

Fig 1: Inversion recovery series of one-dimensional ^{13}C spectra of alanine (0.95M) at 1T from a 3h experiment with one scan per spectrum. Field drifts of up to 1Hz/s of the 1T scanner without temperature stabilization were corrected using a 90° pulse ^{1}H navigator scan before each ^{13}C scan.

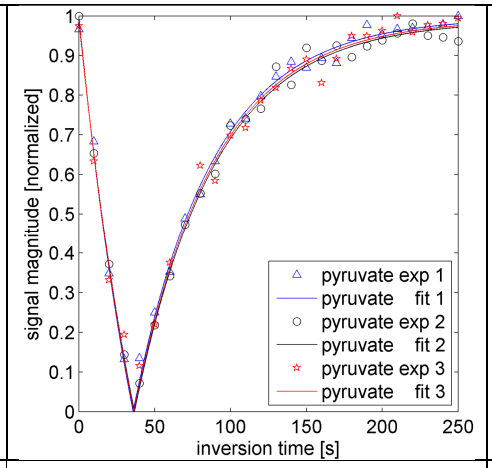

Fig 2: Normalized absolute signals corresponding to three experiments performed at 1T. Data were line broadened and maxima corrected according to the Rice distribution. Even at low field and low concentration, all experiments show good reproducibility without signal averaging.

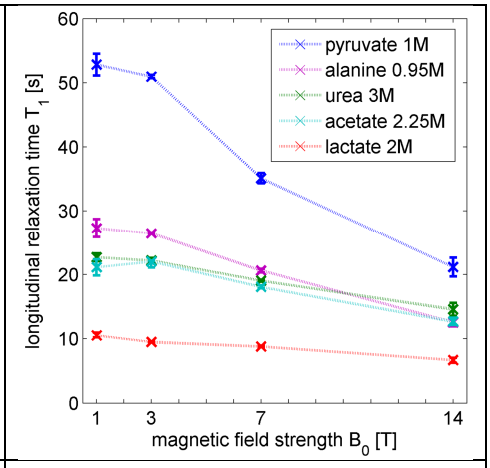

Fig 3: Longitudinal relaxation times T_1 as a function of magnetic field strength B_0. Errors depict 95% confidence intervals from a non-linear fit to theoretical T_1 curves. Within the statistical uncertainty, T_1 decreases with increasing B_0 for all substances. Concentration dependencies have to be studied.

Results: T_1 times were measured for all five compounds at all four fields, each IR sequence taking between 1h and 3h depending on the expected T_1. Temperature dependent magnetic field drifts at the 1T Aspect scanner of up to 1 Hz per second were successfully compensated by performing a 90° pulse proton navigator scan during the TR directly before each ^{13}C scan determining the actual ^{13}C resonance frequency without disturbing the ^{13}C relaxation mechanism (see fig. 1). The application of line broadening and the correction of maxima according to the Rice distribution allowed achieving sufficient low measurement uncertainties with just one scan per TI even at relatively low SNR (see fig. 1 and 2). Reproducibility was shown by performing the same IR experiment for the same sample several times (see fig. 2). Within the statistical uncertainty, we found that T_1 decreases with increasing B_0 for all five substances from 1T over 3T and 7T to 14T.

Conclusion and Discussion: The T_1 times for acetate are comparable to the ones measured from Miéville et al. for a 3M solution in D_20 using the shuttling technique [7]. The T_1 for pyruvate at 1T is comparable to the one measured by Chattergoon et al. using hyperpolarized field cycling. The goal of this study was to investigate T_1 times for a larger number of frequently used hyperpolarization agents under comparable experimental conditions at all field strengths currently clinically available. While pH and temperature could be held constant, concentrations were initially chosen to avoid solubility problems for each compound separately. A series of current experiments studies the dependence of T_1 on compound concentration and TRIS buffer concentration to also allow for a comparison between different compounds. Planning of hyperpolarized experiments could not only take into account the spectral resolution dependency on B_0, but could also consider the type of biological information that can be extracted from the varying duration of the experiment due to the T_1 dependency of the ^{13}C hyperpolarized agent on B_0.

References: [1] Brindle KM et al. MRM 66 (2011) 505 [2] von Morze C et al. JMRI 33 (2011) 692 [3] Bastiaansen et al. BBA (2013) 4171 [4] Coffey A et al. JMR (2013) in press [5] Koay CG et al. JMR 179 (2006) 317 [6] Chattergoon N et al. CMMI 8 (2012) 57 [7] Miéville P et al. JMR 210 (2011) 137. **Acknowledge:** BMBF # 13EZ1114