Measuring polarization using asymmetry of hyperpolarized [1,2-^{13}C]Pyr doublets

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Background: Absolute quantitation is critical for fully interpreting in vivo hyperpolarized metabolic imaging data, and a necessary parameter is the liquid-state polarization of the injected substrate. Lau *et al.* recently published a study suggesting polarization can be obtained by calculating the asymmetry of the C_2 doublet, a_{C2}, arising from the 1% naturally abundant [1,2-^{13}C]Pyr in any hyperpolarized [1-^{13}C]Pyr sample[1]. The paper provided an experimentally derived mapping between a_{C2} and instantaneous polarization. Here we present a more complete analytical analysis showing the actual case is more complicated, and a single time-point measurement of the C_2 doublet asymmetry alone yields an unambiguous measure of neither the initial nor instantaneous polarization.

Theory: Noting that the usual high temperature NMR approximate is invalid for hyperpolarized case, the spin density operator for a sample exiting a polarizer is given by

$$\hat{\sigma}(0) = \tfrac{1}{4}\hat{E} + \tfrac{1}{2}P_C\hat{I}_z + \tfrac{1}{2}P_C\hat{S}_z + \tfrac{1}{2}P_C^2 2\hat{I}_z\hat{S}_z$$

where P_C is the initial polarization for both the C_1 and C_2 carbons.

The I_ZS_Z term, negligible at thermal equilibrium, is significant in the hyperpolarized case and is the dominant source of initial asymmetry of the doublet peaks. Following Lau et al, we define the asymmetry of the C_2 doublet as a_{C2}=(downfield-upfield peak)/(downfield+upfield peak). Starting from the density operator given above and keeping track of the terms due to hyperpolarization, residual strong coupling characteristics at 3T of the J-coupled C_1-C_2 Pyr peaks, and the longitudinal relaxation rates for the two peaks of the C_2 doublet (shown by experiments to differ[1]), the more complete expression for a_{C2} following a pulse and acquire pulse sequence is

$$a_{C2} \approx \frac{e^{-\Delta t/T_1^b} - e^{-\Delta t/T_1^a}}{e^{-\Delta t/T_1^b} + e^{-\Delta t/T_1^a}} + P_C\cos(\phi) + \sin(\theta)$$

where ϕ is the flip angle given to the C_1 doublet, P_C is the initial carbon polarization, Δt is the time of the measurement relative to the sample exiting the polarizer, $\sin(\theta)$ is the standard term arising from strong coupling, and T_1^a and T_1^b are the longitudinal relaxation rates for the upfield and downfield peaks of the C_2 doublet. Full analysis shows the equilibrium asymmetry due to small strong coupling effects ($a_{eq} = \sin(\theta) = 0.057$) is negligible for polarizations above a few %, and the optimum sequence for measurement of a_{C2} employs a 90º excitation of C_2 doublet and 0º excitation of the C_1 doublet, rather than the same small flip angle for both as employed by Lau.

Simulations and Experimental Results: The plots below show simulations for a_{C2} versus initial polarization as parameterized by the time delay between the sample exiting the polarizer and the time of the measurement (Fig. 1a), and a_{C2} versus instantaneous polarization as parameterized by the polarization at time t=0 (Fig. 1b). Experimental data (80 mM [1-^{13}C]Pyr hyperpolarized to ~25% using an Oxford Instruments HyperSense system) acquired with a 32μs hard RF pulse, 5.6° flip angle on both C_1 and C_2 resonances with TR= 3s are shown in Fig 1c.

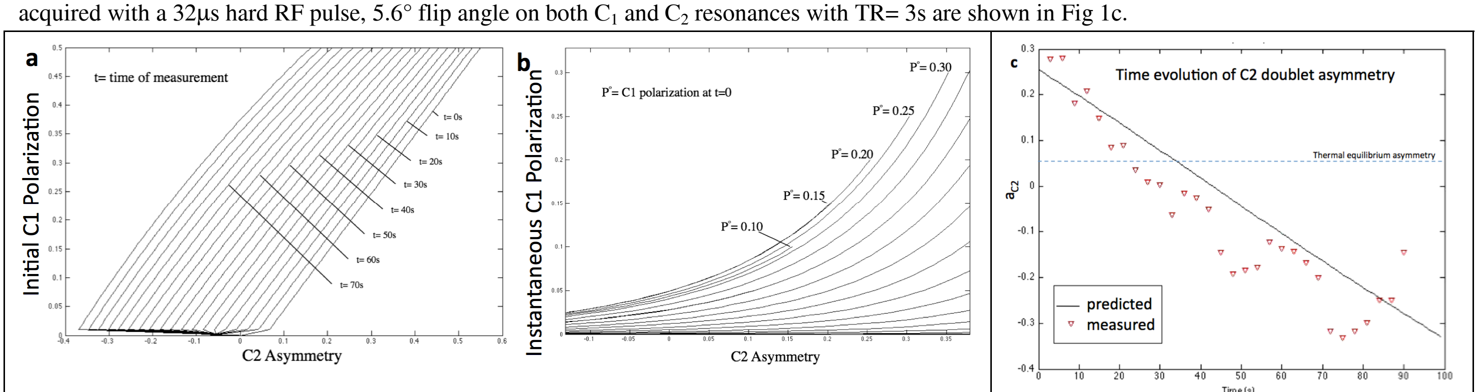

Figure 1. Theoretical family of curves corresponding to (**a**) a_{C2} versus initial C_1 polarization (parameterized by time of measurement) and (**b**) a_{C2} versus instantaneous C_1 polarization (parameterized by the initial polarization). (**c**) Experimental data and predicted curve showing good agreement for time dependence of a_{C2} (80 mM [1-^{13}C]Pyr, ~25% polarization, 5.6° flip angle on both C_1 and C_2 resonances, TR= 3s). Note, $a_{C2,}$ whose time dependence is dominated by the differential upfield and downfield T1 decay times, is only predicted to approach the thermal equilibrium value 0.057 at much later time points (not shown on plot).

Conclusions: The instantaneous polarization versus C_2 asymmetry, a_{C2}, is given by a family of curves parameterized by the polarization at t=0, with the differential peak relaxation times accounting for the dominant time-dependence of this parameter. Based on the derived model, using flip angles of 90^0 and 0º for the C_2 and C_1 peaks respectively yields optimum measurement of a_{C2}, but the critical parameter needed for absolute quantitation is the effective Pyr T_1 relaxation times. In practice, knowledge of the relaxation rates is further complicated by differing T_1s at high (in the 3T scanner) and low (adjacent to the polarizer) magnetic fields.

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References: 1. Lau, J. Y. C., Chen, A. P., Gu, Y.-P. & Cunningham, C. H.. *NMR Biomed.* **26,** 1233–1241 (2013).