Gradient-Enhanced Effectively Decoupled INEPT (GREEDI)

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Background: Polarization transfer methods provide improved detection of ^{13}C nuclei directly bonded to protons, however SAR-intensive decoupling makes efficient in vivo measurements difficult. Here we propose an improved inverse-detection sequence for CH spin systems, which avoids the need for high-power decoupling. The targeted application for ^{13}C-^{1}H coherence transfer is enhanced imaging of [2-^{13}C]Lac and [2-^{13}C]Ala, metabolic products of hyperpolarized [2-^{13}C]Pyr. A reversed sequence providing ^{1}H-^{13}C coherence transfer may also prove useful for improved detection of brain ^{13}C-labeled substrates following the infusion of thermally polarized ^{13}C-glucose of ^{13}C-acetate[1].

Hyperpolarized 13C MRS: Hyperpolarized [2-^{13}C]Pyr provides additional mitochondrial metabolic information not available with [1-^{13}C]Pyr, however the resulting [2-^{13}C]-Lac and –Ala peaks are doublets with a shortened T_1 relaxation times, making measurements unfavorable compared to their C1-labeled counterparts. Extending the work of Mishkovsky et al.[2], large Lac and Ala CH coupling constants (J~150Hz) can be exploited for indirect detection using conventional gradient-enhanced reverse Insensitive Nuclei Enhanced by Polarization Transfer (INEPT) ^{13}C-^{1}H pulse sequence. The proposed new sequence, Gradient- Enhanced Effectively Decoupled INEPT (GREEDI), adds an extra delay (labeled t_2) and dephasing gradient (G_0) inserted before the first ^{1}H pulse and adds a final ^{13}C pulse to call back, as anti-phase magnetization, the typically lost double- and zero-quantum coherences. The sum of the in-phase (conventional INEPT coherence pathway) and the anti-phase terms (GREEDI modification) results in a singlet peak at twice the amplitude of the original doublet. The sign of the final ^{13}C pulse determines whether the upper or lower doublet peak is selected. Filtering of uncoupled nuclei (e.g. water) is provided by the dephasing gradients G_0, G_1, G_2 with the relation G_1=-4G_0=4G_2 yielding maximum coherence transfer ($\gamma_H/\gamma_C \sim 4$). The absence of 180^0 pulses decreases sensitivity to B_1 inhomogeneities. Chemical shift evolution can be neglected during the inter pulse delays when only a single component (e.g. Lac or Ala) is imaged. Because our clinical scanner lacks hardware needed for simultaneous ^{1}H and ^{13}C excitation, we used a 600 MHz Varian Inova spectrometer to demonstrate proof of concept for the new sequence using a thermally polarized [2-^{13}C]Lac sample (1 M in D_20). Fig. 1 shows the theoretical (b) and experimental (c) results.

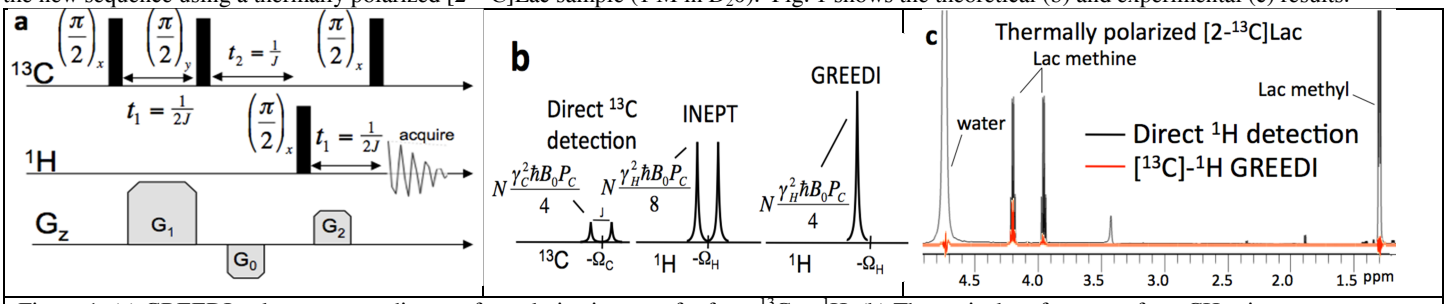

Figure 1. (a) GREEDI pulse sequence diagram for polarization transfer from ^{13}C to ^{1}H. (b) Theoretical performance for a CH spin system (P_c=carbon polarization). (c) Representative spectra for direct-^{1}H and GREEDI-^{1}H detection. GREEDI results show excellent water suppression, doubling of the up-field Lac methine peak, and elimination of the down-field peak. In this thermally polarized case the ^{1}H Lac methine signal decreases by 4x (low ^{13}C polarization), in contrast to the hyperpolarized ^{13}C case where the ^{1}H signal is expected to be greatly enhanced. Frequency selective ^{13}C RF pulses can be used to preserve magnetization from other ^{13}C resonances (e.g. Pyr). Imaging gradients are also easily added for the ^{1}H detection.

Thermally polarized ^{13}C MRS: Figure 2 shows the reversed sequence (with experimental performance) for transferring coherence from ^{1}H to ^{13}C nuclei. Modifications needed for in vivo use include timing adjustments to accommodate both CH and CH_2 spin systems and additional 180º refocusing pulses to increase spectral bandwidth. Such an approach may prove useful for ^{13}C-brain studies where high-power decoupling in regions such as the prefrontal cortex is prohibitive.

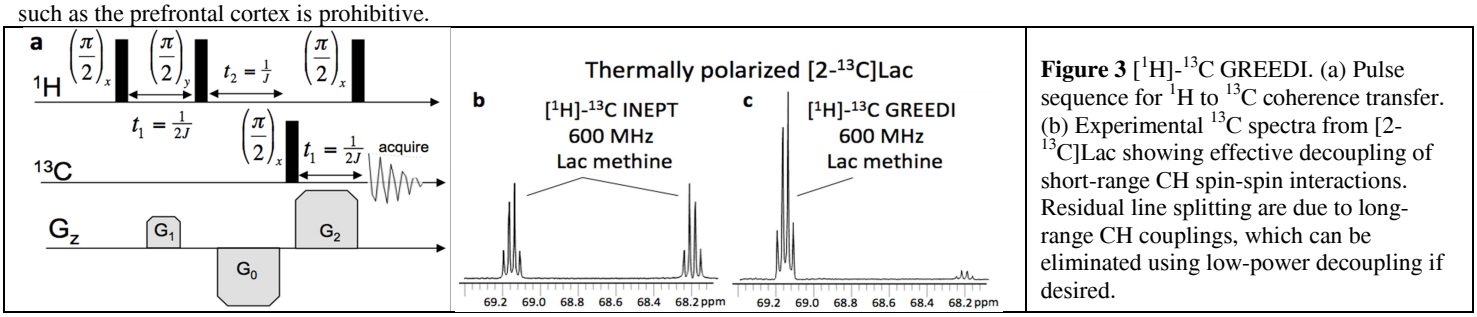

Figure 3 [^{1}H]-^{13}C GREEDI. (a) Pulse sequence for ^{1}H to ^{13}C coherence transfer. (b) Experimental ^{13}C spectra from [2-^{13}C]Lac showing effective decoupling of short-range CH spin-spin interactions. Residual line splitting are due to long-range CH couplings, which can be eliminated using low-power decoupling if desired.

Conclusion: The proposed modified INEPT sequence, GREEDI, eliminates splitting due to short-range ^{13}C-^{1}H J-coupling, while providing a $\sqrt{2}$ SNR gain without the need for proton decoupling. The targeted applications are enhanced imaging of [2-^{13}C]Lac and [2-^{13}C]Ala (metabolic products generated by hyperpolarized [2-^{13}C]Pyr), and improved detection of C2, C3, and C4 glutamate and glutamine resonances following infusion of thermally polarized ^{13}C-substrates.

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References:

1. de Graaf, R. A., Rothman, D. L. & Behar, K. L. State of the art direct 13C and indirect 1H-[13C] NMR spectroscopy in vivo. *NMR Biomed.* **24,** 958–972 (2011).
2. Mishkovsky, M., Cheng, T., Comment, A. & Gruetter, R. Localized in vivo hyperpolarization transfer sequences. *Magn. Reson. Med.* **68,** 349–352 (2012).