Simultaneous Hyperpolarization of Multiple 13C Molecules In Vitro & In Vivo: Towards Rapid Metabolite Mapping By MRS & MRI

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Objective: Develop simultaneous hyperpolarization of multiple ^{13}C reagents for fast imaging and spectroscopy of metabolites *in vivo*.

Background: PASADENA (Parahydrogen And Synthesis Allow Dramatically Enhanced Nuclear Alignment) method of enhancing nuclear spin polarization has recently been improved and demonstrated to produce ^{13}C polarizations (P) of order unity for the nascent products of molecular addition by parahydrogen. It is well known that P for a given nucleus is conserved through chemical reactions, relaxing toward the equilibrium value with a characteristic time T_1 of up to several tens of seconds for ^{13}C. Thus, the establishment by any method of a high value of P allows the corresponding sensitivity enhancement to be transported to any location and chemical species that can be reached on this time scale. An initial polarization of at least P = 0.2 has been achieved with several molecular species. Even after 3 times T_1, sufficient time for an injected species to be taken up from the blood and metabolized, the polarization has decayed to $P = 10^{-2}$. Novel fast ^{13}C imaging and spectroscopy sequences are needed for this purpose. At this time, when no rapidly metabolizable PASADENA reagent has been developed, simultaneous hyperpolarization of two or more molecules of distinct chemical shift provides a convenient test system.

Materials and Methods: To facilitate routine PASADENA trials, GE Healthcare, Malmo has developed an automated polarizer for the initial steps of synthesis and polarization transfer, presently installed at Huntington Medical Research Institute, Pasadena. The polarizer was individually optimized for the production of two hyperpolarized water soluble molecules; a: ^{13}C 2-hydroxyethylpropionate , b: ^{13}C sodium cis-fumarate. Since the difference in J couplings for both the molecules is small, it is possible to apply polarization transfer sequence optimized for one to the other with (2-3%) negligible loss in polarization.

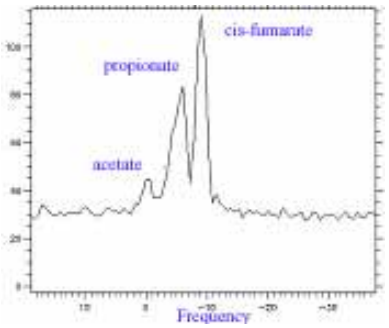

Figure 1. CSI spectra of two simultaneously hyperpolarized (50 mM) ^{13}C molecules along with a non-hyperpolarized 3M acetate phantom as control

Results: The unsaturated precursors of the two molecules are hydrogenated by parahydrogen and hyperpolarized utilizing a general polarization transfer sequence. The formation of dual hyperpolarized product was observed *in vitro* spectroscopically by fast ^{13}C CSI (Fig 1) and fast Multiple Echo 3D FIESTA imaging sequence (Fig 2). Both the sequences are developed at HMRI on a clinical 1.5T GE scanner. These experiments have been extended to *in vivo;* two hyperpolarized reagents are injected in the jugular vein of a rat where both spatial, spectral and dynamic information of multiple hyperpolarized species can be obtained in real time.

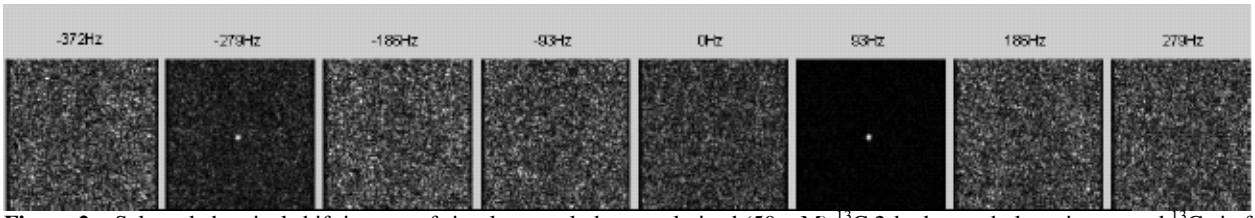

Figure 2. Selected chemical shift images of simultaneously hyperpolarized (50 mM) ^{13}C 2-hydroxyethylpropionate and ^{13}C cis-fumarate.

Conclusion: Successful development of simultaneous hyperpolarization in multiple molecules along with fast detection and imaging capabilities on a clinical 1.5T scanner allows rapid and accurate detection of a) signal intensity, b) anatomical location, c) chemical shift d) dynamic and repeatable time course of multiple chemical species *in vitro* and *in vivo*. Ultrafast imaging and spectroscopy of hyperpolarized metabolites *in vivo* will now be feasible.

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