Separation of C-13 Metabolites with Chemical Shift Imaging

S. B. Reeder[1,2], J. H. Brittain[3], T. M. Grist[1,2], Y-F. Yen[4]

[1]Radiology, University of Wisconsin, Madison, WI, United States, [2]Medical Physics, University of Wisconsin, Madison, WI, United States, [3]Global Applied Science Lab, GE Healthcare, Madison, WI, United States, [4]Global Applied Science Lab, GE Healthcare, Menlo Park, CA, United States

Introduction: The advent hyperpolarized ^{13}C [1] has renewed interest in imaging with this isotope for a variety of applications, including vascular and metabolic flux. C-13 labeled pyruvate and its metabolites, lactate and alanine, have great potential for *in vivo* metabolic imaging, particularly for oncology applications. The NMR spectrum of these three metabolites is relatively sparse, with single peaks for lactate and alanine and two peaks for pyruvate [2]. Sparse data sets such as these may be well suited for chemical shift based imaging methods such as IDEAL (Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation) [3,4,5]. Although *a priori* knowledge of the resonant frequencies of the species is required, separation of species into different images can be achieved with relatively few images acquired at different echo times. In this work, we present a modified IDEAL approach, tailored for separation of ^{13}C labeled pyruvate, lactate and alanine.

Theory: ^{13}C labeled pyruvate is an important probe to interrogate dynamic metabolic processes *in vivo*. The relevant 3.0T spectrum is shown in Fig. 1. Relative to lactate, alanine has a single peak at -242Hz, pyruvate has a main peak at -602Hz and the pyruvate ester lies at -242Hz, all at 3.0T. If the relative area of the peaks of pyruvate are known, the signal from a voxel containing these three species measured at N arbitrary echo times, t_n (n=1, …, N), can be modeled as $s(t_n) = \left(\rho_A e^{i2\pi f_A t_n} + \rho_L e^{i2\pi f_L t_n} + \rho_P \left(r_{P1} e^{i2\pi f_{P1} t_n} + r_{P2} e^{i2\pi f_{P2} t_n}\right)\right) e^{i2\pi\psi t_n}$ (1) where ρ_A, ρ_L, and ρ_P are the total signal contributions from alanine, lactate and pyruvate respectively, f_A, f_L, f_{P1},and f_{P2} are the resonant frequencies of alanine, lactate, the main pyruvate peak and the pyruvate ester peak, and r_{P1} and r_{P2} are the relative fractions of total signal from the two pyruvate peaks(r_{P1}+ r_{P2}=1.0) .The outer phase term results from the local field inhomogeneity (ψ), which can be estimated using an iterative algorithm [1] or measured from separate calibration ^{1}H images. For this discussion, we assume ψ is known and has been demodulated from Eq. 1. Eq. 1 can then be written,

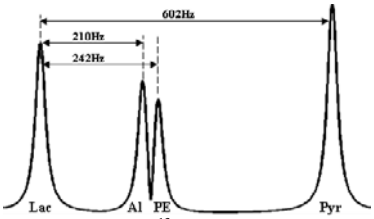

Fig 1: Schematic of ^{13}C spectrum for lactate (Lac), alanine (Ala), and pyruvate (Pyr, PE). Frequency shifts are relative to lactate at 3.0T

$\mathbf{S} = \mathbf{A}\boldsymbol{\rho}$ (2) where $\mathbf{S} = [s(t_1) \quad s(t_2) \quad \ldots \quad s(t_N)]$, $\boldsymbol{\rho} = [\rho_A \quad \rho_L \quad \rho_P]^T$ and $\mathbf{A} = \begin{bmatrix} C_1^A & C_1^L & C_1^P \\ C_2^A & C_2^L & C_2^P \\ \ldots & \ldots & \ldots \\ C_N^A & C_N^L & C_1^P \end{bmatrix}$ with $C_n^A = e^{i2\pi f_A t_n}, C_n^L = e^{i2\pi f_L t_n}, C_n^P = \left(r_{P1} e^{i2\pi f_{P1} t_n} + r_{P2} e^{i2\pi f_{P2} t_n}\right)$ for simplicity of notation. It is important to note that all terms in the coefficient matrix, **A**, are known. Estimates of the three metabolites are then made from the pseudo-inverse of Eq. 2, ie: $\hat{\boldsymbol{\rho}} = \left(\mathbf{A}^H\mathbf{A}\right)^{-1}\mathbf{A}^H\mathbf{S}$ (3) where "H" denotes Hermitian transpose. At least 3 images with different echo times (t_n) are required to decompose the three species.

Echo shifts are chosen to maximize SNR performance of the optimization by calculating the effective number of signal averages (NSA). NSA is easily calculated for each species as the inverse of each diagonal term in the covariance matrix, ie: $NSA_m = 1/\left(\left(\mathbf{A}^H\mathbf{A}\right)^{-1}\right)_{m,m}$ (4) where m=1 (alanine), 2 (lactate), 3 (pyruvate). NSA is plotted for four equally spaced echoes at 3.0T (Fig. 2).

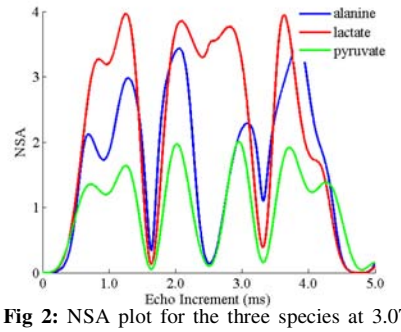

Fig 2: NSA plot for the three species at 3.0T using signal model in Eq. 1 for echoes equally spaced by the indicated "Echo Increment".

Materials and Methods: Imaging was performed on a 3.0T GE Signa MR scanner with a custom built dual-tuned proton-carbon T/R coil. A ^{13}C phantom intended to mimic the *in vivo* ^{13}C spectrum was constructed from three vials doped separately with ^{13}C labeled alanine, lactate, and pyruvate was imaged using a 2D echo planar spectroscopic imaging (EPSI) sequence with fly-back rewind gradients [6]. Image parameters included FOV=6 cm, Δz=20 mm, TR=1s, flip=10^o, 12x12 matrix, 64 echoes spaced by 2.028ms, BW=±6.4kHz. EPSI data were reconstructed using conventional 3D Fourier transformation. For modified IDEAL, a local NSA maximum occurs at a 2ms echo increment (Fig. 2), close to the echo spacing of the EPSI data (2.028ms). Therefore, the first four echoes of the EPSI data were used for the modified IDEAL reconstruction. The relative proportions of the pyruvate peaks were estimated from spectroscopic data (acquired separately): 61% of pyruvate signal was from the main peak and 39% from the ester peak. Images were Fourier transformed in the two spatial dimensions and pixels processed individually using Eq. 3. Chemical shift correction in the readout direction was performed for both methods. Chemical shift correction for pyruvate was difficult with IDEAL because the signal is comprised of two peaks; the average of the two pyruvate frequencies was used.

Results: Figure 3 shows separate pyruvate, lactate, and alanine images generated using EPSI (top row) and IDEAL (bottom row). Good qualitative agreement between separated EPSI and IDEAL metabolite images is seen.

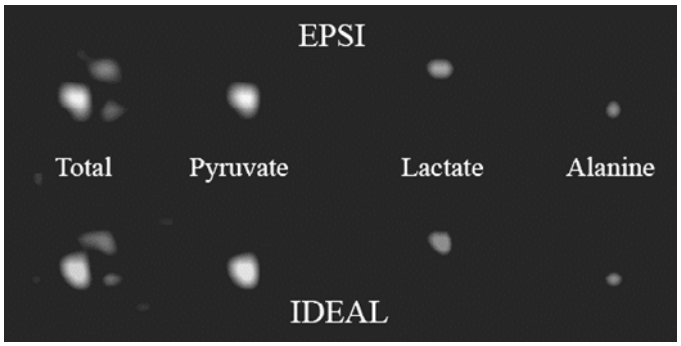

Fig 3: Metabolic ^{13}C images acquired using all 64 echoes with EPSI (top), and only 4 images with IDEAL (bottom). Separate pyruvate, lactate and alanine images show good agreement between EPSI and IDEAL.

Discussion: This study demonstrates the feasibility of a modified chemical shift imaging method (IDEAL) for separation of ^{13}C metabolites, with similar separation as Fourier transformed EPSI. In addition, only 1/16th the number of images was required which would greatly accelerate the overall acquisition time. The modified IDEAL method is able to distinguish alanine from the pyruvate ester through *a priori* knowledge of the relative portions of the two pyruvate peaks. Without this knowledge or knowledge of the metabolite resonant frequencies, separation of metabolites is not possible with chemical shift approaches such as this. Future work will optimize noise analysis, including the potential use of unequally spaced echoes.

References: **1.** Ardenkjaer-Larsen JH, et al. PNAS, 100:10435-39 2003, **2.** In't Zandt, ISMRM 2004 Educ. Program, **3.** Reeder et al, MRM, 51(1): 123-30 2004, **4.** Pineda et al, MRM, 54(3): 625-35 2005, **5.** Reeder et al, MRM 54(3): 636-44 2005, **6.** Cunningham, et al. ISMRM 2005, pg 2512.

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