Spectroscopically selective imaging of hyperpolarized pyruvate and its metabolites using a single-echo variable phase advance method in balanced SSFP

Gopal Varma[1], Xiaoen Wang[1], David C Alsop[1], Rupal Bhatt[2], and Aaron K Grant[1]

[1]*Radiology, Division of MR Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States,* [2]*Medicine, Beth Israel Deaconess Medical Center, Boston, MA, United States*

Introduction The challenge of hyperpolarized imaging is to make use of the magnetization within its lifetime. As with MRI in general, this often leads to a trade-off between spatial and temporal resolution in dynamic imaging. The utility of dynamic hyperpolarized pyruvate imaging for tumor diagnosis lies in inferring metabolic information via its conversion to/exchange with lactate, pyruvate hydrate, alanine and bicarbonate. Some current approaches to metabolic imaging include echo-planar spectroscopic imaging in conjunction with compressed sensing [1], spatial-spectral pulses combined with spiral readouts [2], multi-echo techniques [3], and spiral CSI [4]. In hyperpolarized imaging, refocused pulse sequences such as spin-echo and balanced steady-state free precession (bSSFP) offer SNR gains relative to gradient echo methods because the magnetization decays with T_2 rather than T_2^*, increasing the available sampling time at a given flip angle and improving the SNR by a factor $\sim(T_2/T_2^*)^{1/2}$. Several proposals for spectroscopically selective imaging with bSSFP have been put forth, including multi-echo techniques [5,6] and methods that exploit the 'bright band' phenomenon to selectively excite a single metabolite [7,8]. An alternative approach is to exploit the dependence of the bSSFP signal intensity on the phase advance φ between successive RF pulses. With suitable choice of TR, each metabolite's signal has a distinct dependence on the phase advance. By acquiring a series of images at different phase advance values it is possible to extract images of each metabolite. Off-resonance effects can be corrected during the reconstruction process.

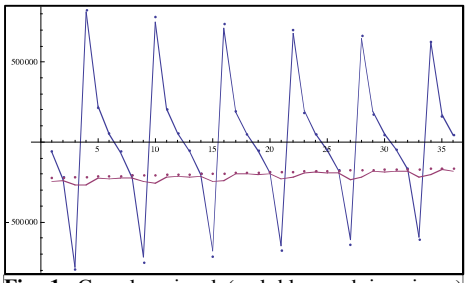

Fig. 1: Complex signal (real=blue, red=imaginary) over 36 frames at 6 repeated φ values. Lines show S~exp(-i[φ+2πΔ.TR]/2).csc([φ+2πΔ.TR]/2), points are data.

Theory At sufficiently low flip angles (FA), the bSSFP signal as a function of off-resonance shows a change in sign or singular point (SP) every 1/TR, which changes based on the RF phase advance, φ. As a function of φ and the chemical shift Δ, the bSSFP signal intensity is given approximately by exp(-i[φ+2πΔ.TR]/2).csc([φ+2πΔ.TR]/2) . Off-resonance effects can be incorporated by replacing Δ with Δ+δf, where δf is the local ^{13}C frequency shift. The combined signal, S, from *m* metabolites will show *m* SPs every 2π, with SPs separated based on the TR and the chemical shift values $\Delta_{1,2,\ldots m}$. The individual metabolite signals can be determined by sampling S at several values of φ and fitting the result to a sum of metabolite profiles. Explicitly, the metabolite signals μ_k are computed from the signals S_l measured at the *k* values of φ from a matrix equation S=Mμ, where M_{ij}=exp(-i[φ_i+2πΔ_j.TR]/2).csc([φ_i+2πΔ_j.TR]/2).

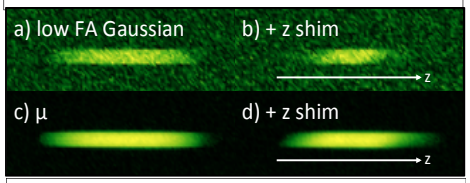

Fig. 2: Phantom images acquired with and without an applied z-gradient. a-b) Images from Gaussian modulated bSSFP; c-d) Images reconstructed from multiple phase-advance method.

Methods Data were acquired on a 9.4T Bruker scanner using an 84mm volume coil for ^{1}H imaging and a custom-built ^{13}C saddle coil. A bSSFP sequence was modified to allow modulation of the FAs based on a Fermi profile. Several images were acquired successively, each with a distinct value of the RF phase advance φ. The bSSFP profile was initially probed in ^{13}C-1-acetate phantom images using a maximum FA~30°, 48x256 (frequency x phase) matrix, 1mm^2 resolution, 10mm slice, TR=1.666ms over 36 frames with φ cycling through values 210; 270; 330; 30; 90; 150°. To explore off-resonance sensitivity, coronal images images were acquired (1) using a Gaussian modulated low-FA bSSFP at φ=0 and (2) with the 6 φ values listed above, both before and after application of a z shim gradient. To obtain images of the acetate magnetization μ, a least squares fit to the data was calculated at each pixel, where the off-resonance, δ*f* ,was allowed to vary by +/-50Hz to minimize the residuals of the fit. A multi-metabolite phantom was prepared using 4 NMR tubes in agar containing aqueous solutions of: bicarbonate; sodium pyruvate; pyruvic acid; lactate. Chemical shifts were determined with a PRESS acquisition, and TR was set to 2.763ms to ensure separation of the metabolite singular points. Data were acquired at 10 φ values to reconstruct the 5 spectral lines in the phantom, allowing δ*f* to float by +/-5Hz. In vivo data were acquired with IACUC approval from an athymic nude mouse bearing an A498 RCC xenograft tumor using a maximum FA~20°, 48x64 matrix, 1mm^2 resolution and 5mm slice. TR was set to 2.018ms and 8 φ values were calculated to separate lactate, pyruvate hydrate, alanine and pyruvate. This TR ensures optimal separation of pyruvate and lactate, whose singular phase advance values are separated by 180°. 10s after tail vein injection of hyperpolarized pyruvate, 80 frames were acquired in 10.337s.

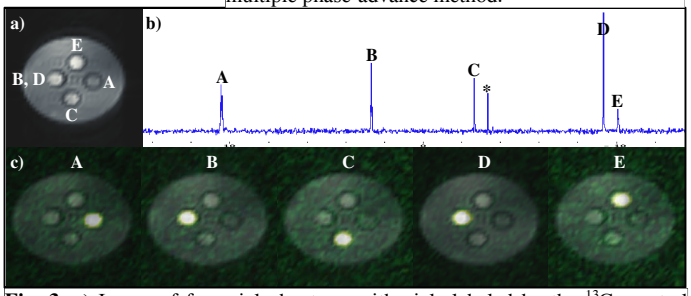

Fig. 3: a) Image of four-vial phantom, with vials labeled by the ^{13}C spectral lines A-E present in each vial. b) Spectrum showing peaks A-E; (*) is an unidentified contaminant. c) Overlays showing chemical-shift selective images.

Results and Discussion The bSSFP signal profile S~exp(-i[φ+2πΔ.TR]/2).csc([φ+2πΔ.TR]/2) is confirmed in the plot of the complex signal as a function of φ (Fig. 1). Fig. 2 illustrates effects of off-resonance on a Gaussian modulated low-tip angle acquisition and a variable phase-advance method. Images reconstructed using the variable phase advance show reduced sensitivity to the applied gradient (Figs. 2c-d). Fig. 3b shows a ^{13}C spectrum from the multi-metabolite phantom, with peaks from lactate (A), pyruvate hydrate (B), sodium pyruvate (C), pyruvic acid (D) and bicarbonate (E) (the low pH of the pyruvic acid solution gives a shift relative to sodium pyruvate and a large hydrate signal). An unknown contaminant (*) contributes no signal to any NMR tube. Employing 10 φ values, the metabolites can be separated (Fig. 3c) even with the small <150Hz splitting between lines D, E. Fig. 4 shows the in vivo results: pyruvate shows prominent intravascular signal (arrow) and signal in tumor (arrowhead). The lactate image shows little intravascular signal, but prominent signal in the tumor. The underlying T_2-image shows a negligible lactate signal in an area of suspected necrosis (arrow).

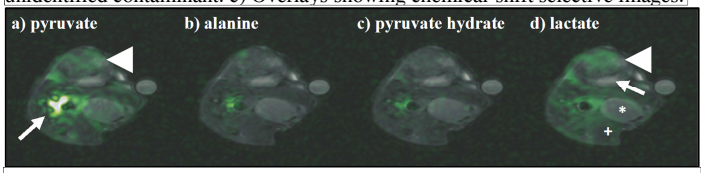

Fig. 4: T_2 weighted axial image in a tumor-bearing mouse with metabolite images overlaid in green. Tumor is visible as an oval-shaped mass at the top of the image (arrowhead). Metabolite images are acquired from ~1s of data.

Conclusions Distinct metabolite contributions can be separated by sampling the bSSFP signal at different φ values. This technique is applied in a phantom containing 5 metabolites and to produce separate pyruvate, alanine, pyruvate hydrate and lactate images following hyperpolarized pyruvate injection in vivo.

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References [1] Hu *et* al, MRM 63(2):312. [2] Lau *et al* MRM 64(5); 1323. [3] Reeder *et al* MRM 51(1):35 [4] Mayer *et al* MRM 62(3):557 [5] Perman *et al* MRI 28(4):459. [6] Leupold *et al* MAGMA 22(4):251. [7] Mansson *et al* MRM 2012 (e-print ahead of publication) [8] von Morze *et al*, Proc. ISMRM 2012, p. 1662.