Spectrally Selective Imaging of Hyperpolarized $^{13}$C Pyruvate with Multi-Echo, Multi-Phase Advance Balanced Steady State Free Precession

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Target audience: A multi-phase advance, multi-echo balanced steady-state free precession (bSSFP) technique is developed to allow spectrally selective imaging. In vivo imaging of hyperpolarized $^{13}$C pyruvate shows its benefit as an alternative for fast, spectrally selective MRI.

Purpose: The proliferation of research involved with hyperpolarized $^{13}$C metabolites has made use of their distinct spectral signatures1. The combination of spectral and spatial information provides further information in such studies, and has led to the development of techniques involving spectral-selective pulses2, multi-echo acquisitions3, and variants of bSSFP that employ a variable phase advance between successive RF excitation pulses to extract spectral information4. bSSFP offers high SNR but suffers from off-resonance banding artifacts5. Multi-echo variants of bSSFP generally require long TRs, resulting in increased off-resonance sensitivity. Multi-phase advance methods can achieve short TRs, but still have undesired sensitivity to off-resonance. We propose a technique that combines a variable phase advance with a short echo train to enable robust separation of metabolites with modest TR and reduced sensitivity to off-resonance.

Methods: Figure 1 provides an illustration of the multi-phase advance, multi-echo (MPME) bSSFP sequence. In this case, three echoes are acquired per TR. The RF pulse amplitudes were modulated, over the phase encodes for a single image, with a Fermi function$^6$. The phase advance value was constant during acquisition of each image, and incremented at the start of each new image. Frequency selective reconstruction of metabolites $m=1,2...M$ was achieved by noting that the pixel-by-pixel image intensities $I_{m}^i$ acquired at phase advance $\phi$ and echo time $\tau$ are linear combinations of the metabolite signals $\mu_m^{i\tau}$ described by the linear equations:

$$I_{m}^i = \sum_{\tau=0}^{N} \sum_{\phi=0}^{M-1} e^{i(\phi-2\pi \frac{\tau}{N} TR)/2} S_{\phi \tau} \mu_m^{i\tau}.$$  

A least-squares solution can be found using the Moore-Penrose pseudo-inverse $\mu = (S^\dagger S)^{-1} S^\dagger I$. Typically, three echoes and two phase advance values are sufficient to resolve pyruvate and its metabolites. Off-resonance sensitivity is minimized by careful choice of TR and the phase advance values. In particular, for a given TR, each metabolite has a 'singular' phase advance where a bright band artifact occurs, resulting in severe off-resonance sensitivity. By appropriate choice of TR, one can arrange, for instance, that some singular points are clustered near $\phi=0^\circ$ whereas others are clustered near $180^\circ$. Acquiring with a short TR and phase advance values near $90^\circ$ and $270^\circ$ minimizes the sensitivity to off-resonance. All data were acquired at $9.4T$ (Bruker Biospec, Billerica MA) after shimming. A $^{13}$C saddle coil was used for phantom experiments and a $20\text{mm}$ surface coil was employed for in vivo data. MPME data were acquired with: $30^\circ$ peak flip angle (phantom/in vivo); $1/1.25\text{mm}^2$ in-plane resolution $48\times256$ matrix; and $4/5\text{mm}$ slice (see figure captions). The phantom was prepared with NMR tubes of acetate, pyruvic acid/pyruvate hydrate and bicarbonate, placed within agar. For in vivo experiments (using methods approved by our Insitutional Animal Care and Use Committee), $^{13}$C pyruvate prepared in a commercial DNP hyperpolarizer (Hypersense, Oxford Instruments, Oxfordshire UK) was injected via tail vein into a nude mouse bearing an A498 cell line xenograft tumor as described previously7. Tumors were immersed in $\text{D}_2\text{O}$ to reduce susceptibility effects at the tissue/air interface. A small ($\approx100\text{μl}$) bolus was injected first, and slice selective spectra were acquired to determine the metabolite frequencies. A second sample was prepared, and $250\text{μl}$ was injected prior to in vivo MPME bSSFP acquisition. TR was set to $3.683\text{ms}$, and the center frequency was adjusted such that the critical phase advance of lactate was $52^\circ$, while the critical phase advances of pyruvate, alanine, and pyruvate hydrate were clustered approximately $180^\circ$ away. Data were acquired continuously with RF phase advances of $131^\circ$ and $334^\circ$, yielding spectrally selective images every $1.9s$. Bicarbonate signal was known to be negligible from slice selective spectral data.

Results and Discussion: Figure 2 shows the results from reconstruction of the phantom data. The relevant metabolite(s) are observed based on the expected value of $f$, and was confirmed by EPSI. From the reconstructed in vivo metabolite images, the expected dynamic features are observed: a strong pyruvate signal within the vasculature and tumor following injection (Figs. 3a, 4a), followed by a persistent lactate signal in the tumor at later time points (Figs. 3b, 4b). The peak lactate SNR with $1.25\text{mm}^2$ resolution on $5\text{mm}$ slice (Fig. 3) was $41.4$. With $1\text{mm}^2$ resolution on a $4\text{mm}$ slice, it was $33.6$.

Conclusions: A MPME bSSFP sequence can provide fast, high resolution hyperpolarized metabolite imaging with good SNR.