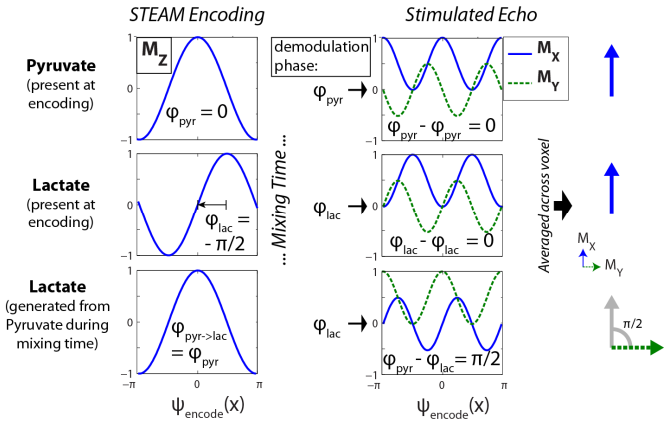
# Hyperpolarized C-13 Metabolic Activity Decomposition with Stimulated-echoes

**P. E. Larson[1], A. B. Kerr[2], J. M. Pauly[2], and D. B. Vigneron[1]**
[1]Radiology and Biomedical Imaging, UC - San Francisco, San Francisco, CA, United States, [2]Electrical Engineering, Stanford University, Stanford, CA, United States

**Introduction:** Metabolic imaging with hyperpolarized $^{13}$C-labelled molecules allows for rapid imaging of in vivo metabolic pathways [1]. In current hyperpolarized carbon-13 imaging methods, the metabolic profile is assumed from indirect observations of converted metabolites. We propose a new method that allows for direct observation of localized metabolic conversion/label exchange for a more accurate metabolic characterization. In this method, the metabolite phase distinguishes between metabolites previously present in the tissue and those generated in the tissue during a mixing interval.

**Methods:** Our method is based on a stimulated-echo acquisition mode (STEAM) sequence [2]. The STEAM encoding, a 90-90 pulse pair with a gradient between, creates a sinusoidal modulation in space, $\cos(x+\varphi)$, along $M_Z$ shown in Fig. 1. This sinusoidal modulation has a phase shift that depends on the resonance frequency and TE: $\varphi = 2\pi f\,TE/2$. Following a mixing time (TM), the final STEAM pulse and gradient refocus this modulation for stationary spins (ie suppresses flowing spins). If a stationary spin changes resonance frequency by $\Delta f$ (ie conversion from [1-$^{13}$C]pyruvate to [1-$^{13}$C]lactate/[1-$^{13}$C]alanine) during TM, it is still refocused, but the resulting transverse magnetization has a phase shift $\Delta\varphi = 2\pi\,\Delta f\,TE/2$. Choosing $\Delta\varphi = \pi/2$ will put the spins generated during TM in quadrature with unconverted spins (Fig. 1), from which they can be separated with a phase-sensitive reconstruction. For pyruvate and lactate at 3T ($\Delta f$ = 385 Hz), we chose TE = 14.2 ms, which gives $\varphi_{lac} = \pi/2$ and also gives $\varphi_{ala} = -\pi/2$.




Hyperpolarized [1-$^{13}$C]pyruvate was injected over 15s and given another 5s to perfuse prior to imaging. Following a non-selective 90-90 encoding, a 1-4cm slab was imaged every 1s for 20s (TM=10ms,1s,2s,… 20s), using a ramping flip angle to use all available magnetization [3]. A symmetrically sampled echo, generated with two adiabatic pulses [4], enabled a phase-sensitive reconstruction. Zero and first-order phase corrections were applied, and $^{13}$C-urea was co-polarized in some experiments [5] to provide a phase reference. This should correct phase shifts caused by homogeneous, bulk motion (ie respiration), since they equally affect all metabolites within a tissue.

*Figure 1*: The STEAM encoding parameters were chosen such that the pyruvate and lactate encoding patterns are out of phase with each other. Pyruvate and lactate present at the encoding are refocused in $M_X$ ($\Delta\varphi = 0$) at the stimulated-echo. However, pyruvate that is converted or exchanges with lactate during the mixing time (TM) is refocused in $M_Y$ ($\Delta\varphi = \pi/2$) at the stimulated-echo.

**Results:**

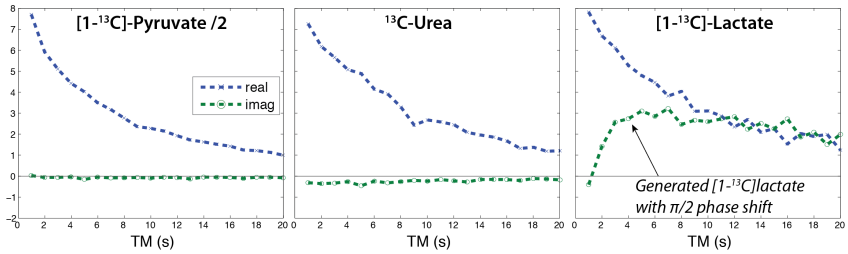



*Figure 2*: Slab in the gut of a normal mouse, showing a large build-up of an imaginary component in lactate – presumably generated from pyruvate – while pyruvate and urea were in-phase, and the real lactate decayed.

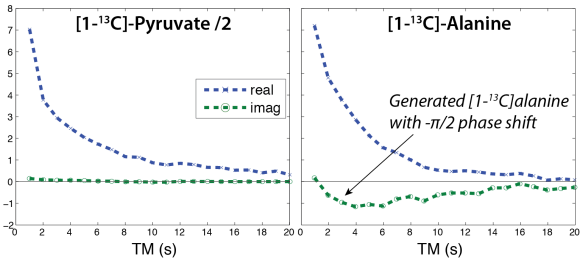



*Figure 3*: Liver slab in a normal mouse, showing a clear build-up of a negative imaginary component in alanine, as expected for alanine generated during TM.

**Conclusion:** We have developed and demonstrated an acquisition and reconstruction method for directly observing metabolic conversion/label exchange. *In vivo* studies demonstrated the ability to detect localized generation of [1-$^{13}$C]lactate and [1-$^{13}$C]alanine from hyperpolarized [1-$^{13}$C]pyruvate via the echo phase. The long $T_1$s (>20 s) of these molecules allow for prolonged observations. The STEAM-based sequence also selectively images only stationary spins, such as those within tissue, and suppresses any flowing metabolites. This novel approach is, to the best of our knowledge, the first to directly image in vivo metabolic conversion.

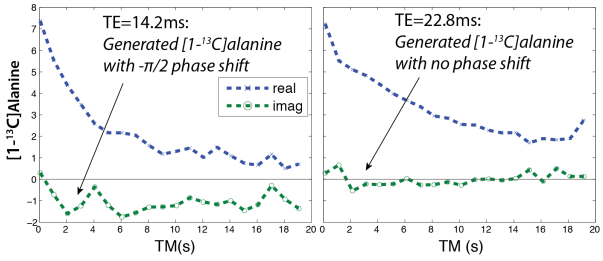



*Figure 4*: In successive experiments, $\varphi_{ala}$ was modulated. This showed no clear imaginary alanine component with $\varphi_{ala}$=0 (right), unlike $\varphi_{ala} = -\pi/2$ (left).

**References**: [1] Ardenkjaer-Larsen JK, et al. PNAS 2003; 100: 10158-63. [2] Frahm J, et al. JMR 1985; 64: 81-93. [3] Zhao L, et al. JMRB 1996; 113: 179-83. [4] Cunningham CH, et al. JMR 2007; 187:357-62. [5] Wilson DM, et al. JMR 2010; 205:141-7.

*Acknowledgments: Funding from NIH K99 EB012064, R01 EB007588 and American Cancer Society PF-09-036-01-CCE.*