Simultaneous Measurement Carbon-13 MR Spin-Relaxation, Diffusion, and Kinetic Parameters

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Introduction: Magnetic resonance spectroscopy (MRS) of hyperpolarized substrates is a powerful tool for investigating tissue metabolism and kinetics in vivo. In addition to detecting increased $K_{\text{PYR-LAC}}$ in tumors using MAD-STEAM, we recently showed that the $T_{1,\text{Eff}}$ of lactate observed after infusion of hyperpolarized pyruvate was significantly shorter in tumors, suggesting a different cellular environment of lactate, in addition to increased $K_{\text{PYR-LAC}}$. However, the $T_{1,\text{Eff}}$ of lactate as measured using the existing method is subject to both spin-relaxation and diffusion effects. We modified the MAD-STEAM pulse sequence to include gradient strength.

Methods: STEAM in the presence of metabolic conversion creates a phase shift dependent on the resonance frequency and echo time ($TE$). $\Delta \varphi = 2\pi fTE/2$ which can be used to “phase tag” metabolites and directly observe real-time metabolism. STEAM can concurrently remove signals from bulk flowing spins, providing improve contrast to cellular metabolism. For validation experiments, $TE=13$ms was chosen such that $\Delta \varphi_{\text{PYR-Hyd}} = \pi/2$, shown in Figure 2. In vivo data was acquired with $TE=14$ms such that $\Delta \varphi_{\text{PYR-LAC}} = \pi/2$. With this information the $T_{1,\text{Eff}}$ and $K_{\text{PYR-LAC}}$ were calculated using MAD. Since $S(t) \propto e^{-t/T_1} e^{-b(t)D}$, the $1/T_{1,\text{Eff}}, = 1/T_{1,\text{x}} + (\gamma G_0)^2 ADC_x$, such that the ADCs and $T_1$s can be estimated by varying the diffusion gradient strength.

Results & Discussion: The measurement of $T_{1,\text{Eff}}$ is a combination of both relaxation and diffusion effects, which can be separated using the pulse sequence shown in Figure 1. In Table 1, we observed a decrease in the $T_1$ relaxation measurements with the addition of GAD and decreases in the ADCs values at cooler temperatures. Hyperpolarized carbon-13 diffusion coefficients, $T_1$ relaxation, and rates of conversion and exchange were measured simultaneously for the first time in vivo, shown in Figure 3. Furthermore, the ADC of lactate that was converted from pyruvate via the intracellular LDH enzyme during the experiment was separated from the ADC of other lactate molecules.

![Figure 1](image1.png)  
**Figure 1.** Dynamic-diffusion sensitive MAD-STEAM sequence. All data was acquired with slab selection in x, 2D, 1sec temporal resolution, 256 spectral points, 2.5 kHz spectral bandwidth, and adiabatic double spin echo.

![Figure 2](image2.png)  
**Figure 2.** Diffusion, relaxation, and conversion parameters from a diffusion sensitive MAD-STEAM in a syringe (TE=14ms, b-values: 65-1734s/mm²). $K_{\text{PYR-LAC}}$ denotes the ADC of lactate that has not gone through conversion via the LDH enzyme. $ADC_{\text{New(lac)}}$ denotes the ADC of lactate that has not gone through conversion. $ADC_{\text{Orig(lac)}}$ denotes the ADC of lactate that was converted from pyruvate.

![Figure 3](image3.png)  
**Figure 3.** Diffusion, relaxation, and conversion parameters in vivo (TE=14ms, b-values: 65-1734s/mm²). $ADC_{\text{Orig(lac)}}$ denotes the ADC of lactate that has not gone through conversion. $ADC_{\text{New(lac)}}$ denotes the ADC of lactate that has not gone through conversion. $ADC_{\text{Orig(lac)}}$ denotes the ADC of lactate that was converted from pyruvate.

Conclusion: With the removal of confounding vascular signals, improved accuracy of estimation of real-time conversion rates, and simultaneous measurements of ADCs and $T_1$s, the developed approach provides new quantitative measures of relaxation, diffusion, and conversion rates. The results of this study demonstrate the potential value of this technique to better measure and understand tumor metabolic changes and the cellular environment with carcinogenesis, progression and response to therapy.