Volumetric quantitation of metabolic kinetics of hyperpolarized [1-^{13}C]pyruvate using multiband RF pulses

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Introduction

Although hyperpolarized ^{13}C spectroscopic imaging has been used to visualize metabolic activities in various organs and pathologies, robust quantification of metabolic kinetics remains an important area of investigation [1]. Xu *et al* [2] demonstrated an efficient quantification approach employing an inflow-based single-slice dynamic spiral chemical shift imaging (CSI) acquisition such that metabolic kinetics, including saturation effects, can be quantified with a single bolus injection. The ^{13}C labeling of lactate and alanine after a bolus injection of [1-^{13}C]pyruvate were modeled using a Michaelis–Menten-like formulation, with the resulting estimated apparent maximal reaction velocity V_{max} and apparent Michaelis constant K_M being unbiased with respect to substrate dose, bolus shape and duration.

Given the heterogeneity of metabolic kinetics within an organ or pathology, it is desirable to have a volumetric quantification method that can measure the kinetics in 3D/multiple slices following a single pyruvate injection. The single-slice dynamic acquisition in [2] used a 90° flip angle for all metabolites, relying on inflow of Pyr to replenish the slice each TR. The extension to the volumetric case necessitates a low flip angle for Pyr to preserve its magnetization while exciting a 90° flip angle for the metabolic products, hence multiband RF pulses are used for the 3D dynamic acquisition. This work extends the single-slice quantification method in [2] to the volumetric case and applies it to measuring apparent maximal reaction velocity V_{max} in rat kidney and liver.

Methods

All measurements were performed on a GE 3T MR scanner with a high-performance insert gradient coil (operating at 292 mT/m, 1015 mT/m/ms). A custom-built dual-tuned ^{1}H/^{13}C transmit/receive quadrature rat coil (dia=80 mm, length=90mm) was used for RF excitation and signal reception. Healthy male Wistar rats (412±24 g weight, n=3) were injected in a tail vein with approximately 3.2 ml of 125-mM solution of [1-^{13}C]-pyruvate. The samples were hyperpolarized via Dynamic Nuclear Polarization using HyperSense (Oxford Instruments Molecular Biotools, Oxford, UK), achieving approximately 20% liquid state polarization.

Two multiband spectral-spatial RF excitation pulses were designed as described in [3] – RF1 with a 5º flip angle for Pyr and stopbands at lactate (Lac) and alanine (Ala), and another pulse RF2 with a 90º flip angle for Lac and Ala and a stopband at Pyr. The stopband ripple was less than the passband ripple of the other pulse. Both RF pulses were designed for the same slab-select gradient waveform (EPI flyback design) with maximum gradient amplitude of 9.795 G/cm, duration=17.78ms for 4cm slab excitation. The RF2 pulse amplitude was scaled every TR and combined with RF1 in real-time on the scanner to achieve a variable flip angle scheme upto 90° for Lac and Ala while keeping a constant 5° flip angle on Pyr.

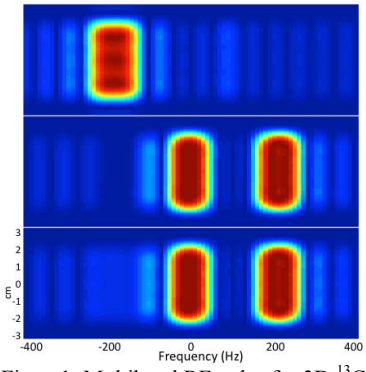

Figure1: Multiband RF pulse for 3D ^{13}C CSI. Top=RF1 with 5° on Pyr (-180Hz). Center=RF2 with 90° on Lac (210Hz) and Ala (0Hz). Bottom=RF1 and RF2 combined. Scale for RF1 is [0 0.09], others is [0 1]. The peak B1 was 0.73G for the combined pulse.

Dynamic 3D ^{13}C data were acquired from a 6 cm slab including the kidney and liver. Imaging parameters were: FOV=80×80×60mm^3, 5×5×5mm^3 nominal resolution, 12 phase-encoding steps per volume, TR=6.27s, to allow 4.55 s reaction window time every TR for metabolic conversion. Dynamic 2D ^{13}C CSI data from 1-cm thick slices through liver and kidney were also acquired from the same animals following separate injections. The 2D slice locations matched the corresponding slices in the 3D acquisition. The 2D method used a single-shot spiral acquisition, with a 90° flip angle on all metabolites, TR=5s and the same 5mm in-plane resolution and 4.55s reaction window time as the 3D. Both methods also applied non-slice-selective lactate saturation every TR to eliminate inflowing signal. Imaging was started coincident with the Pyr injection.

The dynamic data were analyzed using the saturable kinetics model described in [2]. For modeling the 3D data, a new parameter was added to the model: pyruvate transit time (PTT), corresponding to the average duration a pyruvate spin is affected by RF excitation. PTT is used to estimate the effect of the RF sampling from prior excitations on inflowing Pyr spins magnetization.

Results and Discussion

Figure 1 shows the spectral-spatial profile of the multiband RF pulses. The 90° flip angle on Lac and Ala every TR obviates the effect of T_1 decay while the low flip angle on Pyr preserves longitudinal magnetization for later time points. The cumulative effect of 12 excitations of 5° each leads to an effective flip angle of approximately 17.2° on Pyr for the volume acquisition (estimated as $\cos^{-1}(\cos^N \alpha_k)$, ignoring any changes in Pyr magnetization during the time between excitations).

Figure 2 shows a representative example of saturable kinetics measured with a single bolus injection in kidney and liver. By an appropriate choice of PTT, a close match is obtained between the estimated apparent V_{max} and K_M values determined from the 3D acquisition and the corresponding single-slice experiments. Further analysis showed that there exists a value of PTT for which the 2D and 3D estimates of V_{max} and K_M match precisely. Table 1 summarizes the estimated apparent Vmax values in the liver and kidney for the appropriate PTT (PTT_{liver}=2.9±0.1 s/cm, PTT_{kidney}=3.4±0.1 s/cm).

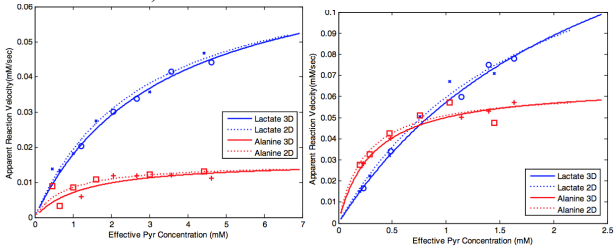

Figure2: Saturable kinetics measured from kidney (left) and liver (right) show consistent results between 2D and 3D.

	V_{max} liver (mM/s)		V_{max} kidney (mM/s)	
Rat ID	Pyr-Lac	Pyr-Ala	Pyr-Lac	Pyr-Ala
H237	0.1775	0.0863	0.0889	0.0222
H235	0.1696	0.0635	0.0740	0.0154
H234	0.2046	0.0777	0.0661	0.0200

This work demonstrates the extension of the single-slice quantification using a Michaelis-Menten-like formulation to the volumetric case using multiband RF pulses, obtaining consistent results for the 2D and 3D acquisitions.

References: [1] Brindle KM *et al* 2011 MRM [2] Xu T et al 2011 NMR Biomed 24:997-1004 [3] Larson P *et al* 2008 JMR 194:121-127

Acknowledgements: NIH grant RR09784, AA05965, AA018681, AA13521-INIA, EB009070