Frequency-domain quantification and interpretation of dynamic hyperpolarized 13C signals

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Introduction: Hyperpolarized 13C imaging provides a wealth of metabolic information within very short time, including substrate perfusion, transport and enzymatically-driven conversion towards downstream metabolites. While early experiments were based on dynamic acquisition of slice-selective FID spectra, or single-time point 2D chemical shift imaging (CSI), recently developed methods allow dynamic acquisition of 3D metabolite images with a time resolution of a few seconds only (1,2). This leads to the question of how to best and most comprehensively quantify and interpret these data?

Similar to standard MRI, absolute quantification of metabolite signals is typically difficult due to uncertainties in experimental factors, such as polarization level, B1 homogeneity, transmitter and receiver gain settings, T1 relaxation, etc. Instead, downstream metabolites are often normalized relative to the detected substrate. More recently, also kinetic modeling has been used to extract quantitative apparent rate constants (3, 4). In this work a novel frequency-domain quantification method is presented for the analysis and interpretation of dynamically acquired hyperpolarized 13C metabolite signals.

Theory and Methods: Enzymatically-driven conversion of 13C pyruvate towards lactate, alanine, and bi-carbonate can to a good approximation be described by a two-side exchange model between the pyruvate substrate (P) and each individual down-stream metabolite X (with X being lactate, alanine, or bi-carbonate); while conversion among the downstream metabolites themselves can to a good approximation be neglected. Assuming the production rate of X is linearly dependent on the substrate concentration P, the conversion can be described by the Bloch-McConnell equation:

$$dX(t)/dt = +k_{P\to X}P(t) - (1-\cos(FA))^{1/TR}\,X(t) - k_{X\to P}X(t) - R_{X,1}X(t) = +k_{P\to X}P(t) - R_{X,eff}X(t) \quad [1]$$

The term $+k_{P\to X}P(t)$ describes enzymatically-driven forward conversion, with $k_{P\to X}$ the forward rate constant, whereas $-R_{X,eff}X(t)$ describes an effective decay including repetitive excitation with flip angle FA and repetition time TR, back-conversion ($k_{X\to P}$) and $R_{X,1} = 1/T_{X,1}$ relaxivity. The model accounts for variable in- and outflow of pyruvate, but assumes them to be identical for X. Transforming above equation from time to frequency domain results in:

$$i\omega x(\omega) = +k_{P\to X}p(\omega) - R_{X,eff}x(\omega),\ with:\ x(\omega) = \int X(t)e^{i\omega t}dt,\ p(\omega) = \int P(t)e^{i\omega t}dt \quad [2]$$

Given the time-resolved metabolite signals, both [1] and [2] result in an over-determined system of linear equations for $k_{P\to X}$ and $R_{X,eff}$, which can be solved in a least-squares sense via Moore-Penrose matrix inversion. From the two formulations, the frequency description [2] is advantageous because it circumvents time differentiation of X, which generally results in noise amplification. As demonstrated in Fig. 1, the frequency domain representation provides a natural and effective way of compressing the dynamic metabolite signal traces into a few dominant Fourier coefficients around DC. Interestingly, for $\omega = 0$, this also provides a physical interpretation of DC ratio of the signals x and p according to:

$$0 = +k_{P\to X}p(0) - R_{X,eff}x(0), \qquad respectively:\ \frac{\int X(t)dt}{\int P(t)dt} = \frac{x(0)}{p(0)} = \frac{k_{P\to X}}{R_{X,eff}} \quad [3]$$

This in turn can be used to derive analytical expressions for $k_{P\to X}$ and $R_{X,eff}$ according to:

$$k_{P\to X} = i\omega\frac{x(\omega)p(0)}{p(\omega)x(0) - x(\omega)p(0)}, \qquad R_{X,eff} = i\omega\frac{p(\omega)x(0)}{p(\omega)x(0) - x(\omega)p(0)} \quad [4]$$

Hyperpolarized [1-^{13}C]pyruvate experiments were performed using a GE 3T HDx scanner (GEHC, Waukesha, WI) and the DNP HyperSense polarizer (Oxford Instruments, Oxford, UK).

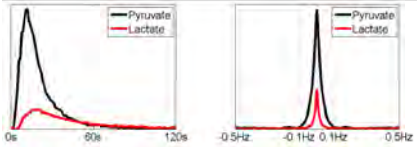

Fig. 1: Typical metabolite signals obtained from slice-selective FID measurements in time (left) and frequency (right) domain illustrating a DC concentrated, sparse frequency content.

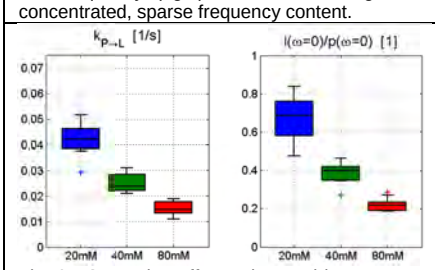

Fig. 2: Saturation effects observed in a pyruvate dose escalation study in an axial slice through the kidney.

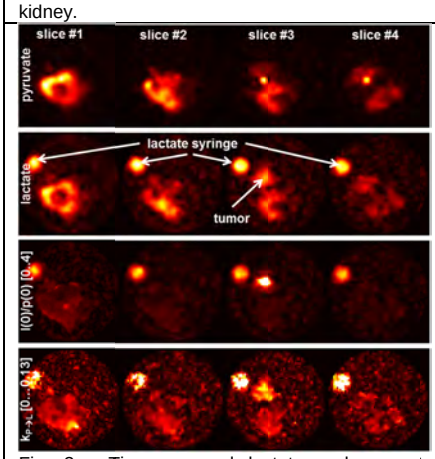

Fig. 3: Time-averaged lactate and pyruvate metabolite maps (top rows) are compared with $l(0)/p(0)$ normalization and $k_{P\to X}$ apparent rate constant quantitation (bottom rows).

Results: Figure 2 shows results obtained from a dose escalation study in rat animal experiments (N=20) using dynamic slice selective FID acquisition (FA=5deg, TR=1s). A quantity of 5ml at various concentrations of hyperpolarized [1-^{13}C]pyruvate was injected into the tail vein of the animals. The left plot quantifies the results in terms of the apparent rate constant $k_{P\to X}$, whereas the right plot uses the DC signal ratio $l(0)/p(0) = k_{P\to X}/R_{X,eff}$ [3]. A similarly saturation effect is observed in both cases.

Figure 3 shows representative results obtained from a dynamic, multi-slice IDEAL spiral CSI (2) study (FA=5deg, 7TEs+1FID, matrix=32x32pts, 32kHz, 4 slices, and 4s CSI time resolution) in rats with subcutaneously implanted MATBIII tumors (N=4). In this case a volume of 2.5ml of 80mM hyperpolarized [1-13C]pyruvate was injected. Perfusion effects appeared significantly reduced in both quantitation methods (bottom rows) relative to the native metabolite maps (top rows). Qualitatively the best SNR and contrast behavior was found using the simple DC ratio, whereas quantitatively the apparent rate constant appeared more consistent.

Discussion and Conclusion: Kinetic modeling in frequency domain provides fast and robust quantification of dynamically acquired 13C metabolite signals with a clear physical interpretation. This is because of i) noise enhancing time differentiation is replaced by simple $i\omega$ multiplication in Fourier space, ii) signal dynamics can efficiently be compressed in frequency space (cf. Fig 1), and iii) high SNR DC information has a clear interpretation [3] and can be used to derive analytical expressions for both $k_{P\to X}$ and $R_{X,eff}$ [4]. Both metrics suppress perfusion and correct for differences in the polarization and receiver gain settings. In addition the apparent rate constants $k_{P\to X}$ also corrects for T1-relaxation effects, signal depletion due to repetitive excitation (TR, FA) and back conversion, as summarized in $R_{X,eff}$ [1].

References: (1) D Mayer et al, JMR 204: 340-345, (2) F Wiesinger et al, MRM: in press. (3) ML Zierhut et al, JMR 202: 85-92. (4) F Wiesinger et al, ISMRM 2010: 3282. (5) HM McConnell et al, J Chem Phys 28: 430-431. **Acknowledgements:** This work was co-funded by BMBF MOBITUM grant number 01EZ0826/7 and 01EZ1114.