Modeling of Pyruvate/Lactate Kinetics Using a Two-Site Exchange Model

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Introduction: Hyperpolarized pyruvate is a promising new tool for non-invasive assessment of metabolism. Following injection of pyruvate, metabolites including lactate, bicarbonate, and alanine are readily observed. The lactate signal has been the focus of much attention, as it is a marker for heightened levels of glycolytic fermentation, a biomarker for cancer. Although the lactate SNR has been shown to correlate well with histological characteristics of prostate cancer in TRAMP mice [1], more quantitative measures of pyruvate/lactate kinetics may be needed in order to assess underlying metabolic fluxes and the corresponding enzyme activities. Previous studies [2] have outlined the use of a two-site exchange model for assessment of pyruvate/lactate exchange rates. Here we extend this discussion to include modeling of the arterial input function, including simultaneous fitting of the input function, the effective T_1 decay rates, and the exchange parameters. In addition, we comment on statistical errors and certain correlated uncertainties arising from the method.

Methods: In Fig. 1 we display a pair of representative pyruvate/lactate data sets acquired as part of a study described in detail elsewhere [3]. Methods were approved by the Institutional Animal Care and Use Committee. Both were acquired in a subcutaneous xenograft model of non-small lung cancer using surface-coil localized carbon-13 spectroscopy. The data on the right were acquired in a mouse that had been treated with dichloroacetate, a drug that upregulates the activity of pyruvate dehydrogenase, thus increasing the availability of acetyl-CoA for the TCA cycle and potentially reducing lactate formation as well as overall levels of lactate.

Pyruvate and lactate magnetization densities M_P, M_L, are dictated by a coupled set of equations:

$$\frac{dM_P}{dt} = -\left(\frac{1}{T_{1,P}^{\text{eff}}} + k_{PL}\right) M_P + k_{LP} M_L + C_{A,P}(t), \quad \frac{dM_L}{dt} = -\left(\frac{1}{T_{1,L}^{\text{eff}}} + k_{LP}\right) M_L + k_{PL} M_P + C_{A,L}(t). \tag{1}$$

In Eq. (1), $T_{1L,P}^{\text{eff}}$ are the effective longitudinal relaxation times of pyruvate and lactate, k_{LP} is the rate of lactate to pyruvate conversion, and k_{PL} is the rate of pyruvate to lactate conversion. $C_{A,P}(t)$ and $C_{A,L}(t)$ are the inputs of pyruvate and lactate magnetization, respectively. The T_1 relaxation rates represent *effective* rates that include the effects ordinary T_1 decay as well venous outflow and the application of repeated low tip-angle RF pulses, both of which give rise, on average, to an exponential decay of the magnetization. Likewise, the quantities k_{PL} and k_{LP} represent effective values averaged over many compartments in the tissue. For simplicity we have omitted metabolites other than pyruvate and lactate, and we have neglected the equilibrium magnetization levels, as these are generally negligible *in vivo.* At the concentrations used for *in vivo* studies, the rates of pyruvate/lactate uptake and interconversion are non-linear functions of the metabolite concentrations. The linear description of Eq. (1) is therefore an approximation that can be used to obtain semi-quantitative estimates of the rate constants.

The model in Eq. (1) was fitted to the data assuming that the arterial input was dominated by pyruvate and that the shape of the input bolus was a given by a gamma-variate function of the form $(t-t_0)^{\alpha} e^{-t/\beta}$. For each parameter set ($T_{1L,P}^{\text{eff}}$, k_{LP}, k_{PL}, α, β and t_0) the system was solved analytically and compared to the data; the fit was optimized using a bound-constrained downhill simplex method implemented in the Mathematica programming language (Wolfram Research, Champaign, IL). Statistical error estimates were obtained by repeatedly adding random Gaussian noise of an amplitude set by the SNR and determining the resulting variation in the best-fit parameters.

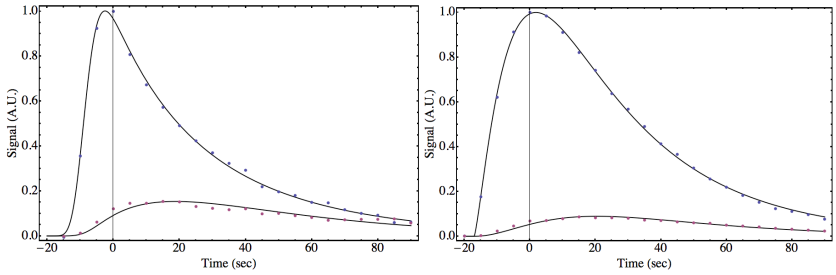

Figure 1. Pyruvate and lactate signal intensities (dots) in control (left) and DCA-treated (right) tumors. Best fits are shown as solid curves.

Results: The solid curves in Fig. 1 show the fits obtained using these methods, together with the data. The best-fit values of the exchange constants are k_{LP}=0.018±0.004 s^{-1} and k_{PL}=0.012±0.001 s^{-1} in the control tumor and k_{LP}=0.021±0.006 s^{-1} and k_{PL}=0.0066±0.0007 s^{-1} in the DCA treated tumor. Although the rates of lactate to pyruvate conversion are consistent within error, the rate of pyruvate to lactate conversion is significantly in the DCA treated tumor. In both cases, the best fit indicates that lactate formation from pyruvate occurs at a higher rate than the reverse reaction, counter to what might be expected following administration of a large bolus of pyruvate. This may be an artifact of the linearized fitting procedure or may be a transient feature of the kinetics in tissue when it is far from equilibrium. In addition, the fitted values of k_{LP} are subject to sizable uncertainties, and the best-fit value is highly correlated with the extracted value of k_{PL}. Indeed, the χ^2 of the fit shows that values of k_{LP} in the range of 0.005 s^{-1} can still lead to a good fit provided that the change in k_{LP} is compensated by a much smaller reduction in k_{PL}.

Conclusions: Two-site exchange models can be used to obtain semi-quantitative assessments of pyruvate/lactate interconversion rates *in vivo*. The simple linear model described here indicates an appreciable reduction in the rate of pyruvate conversion into lactate following administration of DCA. Improved modeling can be achieved by use of more sophisticated data acquisition methods (see, e.g., [4]), such as techniques that separately modulate the pyruvate and lactate magnetization in order to assess uptake and forward and reverse fluxes. Development of these methods is underway.

References: [1] MJ Albers *et al*, "Hyperpolarized 13C Lactate, Pyruvate, and Alanine: Noninvasive Biomarkers for Prostate Cancer Detection and Grading" Cancer Res 2008; **68** 8607-15. [2] SE Day *et al*, "Detecting tumor response to treatment using hyperpolarized 13C magnetic resonance imaging and spectroscopy" Nature Medicine 2007 **13** 1382-1387. [3] AK Grant *et al*, ISMRM 2010. [4] D. Spielman, Proceedings of the 2nd International Workshop on Hyperpolarized Carbon-13, 2009.