Quantifying uncertainty in kinetic modelling parameters of hyperpolarized dynamic nuclear polarization data through the applicaton of Bayesian Inference fitting techniques

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Target audience: Dynamic NMR Spectroscopy and hyperpolarization MR researchers, mathematical modelers, perfusion and MR for cancer researchers.

Introduction: Dynamic nuclear polarization (DNP) is a novel technique for increasing the sensitivity of magnetic resonance spectroscopy and imaging (MRS/MRSI). Intravenous (i.v.) administration of hyperpolarized pyruvate provides a means for quantifying pyruvate-lactate interconversion in living tissues via MRS/MRSIand in oncology, is a potential marker for the efficacy of anti-cancer drugs [1] The rate constant for pyruvate to lactate conversion, k_{pl}, requires mathematical models to extract kinetic parameters, from the spectroscopy data and the quantification of such parameters depends on the mathematical model and the fitting approach used. In this study we determine whether a Bayesian fitting method (previously adopted in the quantification of perfusion from Arterial Spin Labeling [2]) offers improvements in accuracy and robustness compared to common fitting methods such as Nelder-Mead when applied to the quantification of pyruvate to lactate rate constants. Additionally, we use the estimates of the uncertainty in k_{pl} obtained from the Bayesian method to assess whether the variations k_{pl} are the result of fitting error or inter-group variability.

Methods: ^{13}C MRS Experiments: Male, tumor-bearing BDIX rats (250-350g, n=12) were anaesthetized for MR scanning using 1-2% isoflurane at 2 L/min via a nose cone and pyruvate delivered via a femoral vein cannula. The animal was placed in a Bruker 7T MRI system with its temperature maintained at 37oC and respiration rate monitored. Pyruvate was hyperpolarized using a HyperSense system (Oxford Instruments) and 5ml/kg of hyperpolarized ^{13}C-pyruvate (~150 mM) was administered over 13s using a custom MR compatible automated injector[3]. ^{13}C spectroscopic slice localized data (TR=1s, SW=50 ppm, 256 points) were acquired using a Gaussian pulse (20^o flip angle) and a 20 mm ^{13}C/^{1}H surface coil. The MRS raw data was processed using Matlab. Phase sensitive spectra were integrated in the spectral regions of [^{13}C-1]pyruvate, [^{13}C-1]lactate and ^{13}C time response curves were produced for the slice containing the tumor .

Table 1: Priors and initial values for fitting

	Initial values (Nelder–Mead)	Priors (mean±SD) Bayesian
k_{pl} (s^{-1})	0.03	0±30
$k_{lp} + R_L$ (s^{-1})	0.2	0.033±0.01

Data fitting: A precursor product model has been previously shown as the best approach for quantification, k_{pl}, in the absence of an experimentally measured arterial input function (AIF)[4]. This model takes the tumor tissue pyruvate time-course (Pyr(t)) as the input for the lactate time- course (Lac(t)):

$$\mathrm{Lac}(t) = k_{pl}\mathrm{Pyr}(t) \otimes e^{-(k_{lp}+R_L)} \quad (1)$$

where R_L is a lumped parameter incorporating the relaxation times of lactate in the tumor tissue, the flip angle and the repetition time, outflow of lactate to blood; k_{pl} and k_{lp} are the fractional rate constants for the interconversion of pyruvate and lactate in the tumor tissue. All data were fitted using two approaches: (1) by minimizing the root-mean-squared error (RMSE) using a Nelder–Mead nonlinear minimization and initial values for the fitted parameters; (2) using Bayesian Inference with priors given as the mean and standard deviation of a normal distribution (Table 1), with the prior for k_{pl} being effectively non-informative.

Results and discussion: Results show a strong positive correlation for k_{pl} (r=0.99) and $k_s = k_{lp} + R_l$ (r=0.98) values predicted between the two error minimization techniques. Figure 1 shows the RMSE for all data points obtained from the two fitting methods. The Bayesian inference technique consistently fitted the data with statistically significant lower fitting error than the Nelder-Mead nonlinear minimization (P = 0.0006, Student paired t-test). Figure 2a shows the mean ± SD for k_{pl} values in each individual animal obtained from the Bayesian inference fitting technique. The data showed variation in $k_{pl}$was not due to fitting error, as shown by the small error bars but due to inter-animal variability . This is important in distinguishing small variation in kpl.Figure 2b illustrates an example where Bayesian fitting techniques for individual animal data, from a previous study [5], showed a small but significant change in k_{pl} between normoxia and hypoxia conditions. The small error bars obtained from the Bayesian fitting method allows the change kpl to the attributed to a change in oxygenation rather than an error in fitting. This study highlights the need to collect individual control and active condition data and use Bayesian fitting procedures to estimate and investigate the relationship between errors in pyruvate and lactate conversion rate constants due to fitting and inter-animal variability.

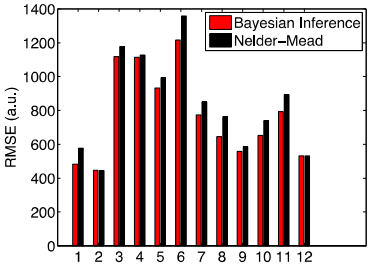

Figure 1: RMSE comparison between Bayesian Inference fitting and Nelder Mead.

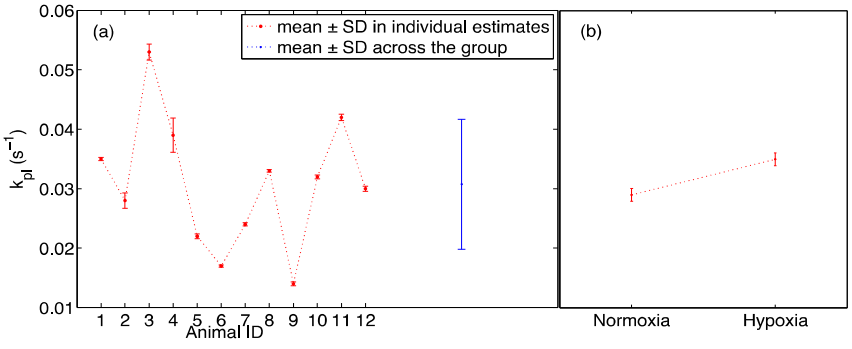

Figure 2: (a) mean ± SD for k_{pl} values in each individual animal (red) together with the mean ± SD for k_{pl} values across the entire group (blue) using Bayesian inference fitting technique (b) Example case with normoxic and hypoxic changes in one animal.

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