A Bayesian Approach to Modeling the Delivery of a Hyperpolarized Substrate

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Introduction

Hyperpolarized (HP) metabolic agents promise to revolutionize our ability to measure flux in vivo. While HP substrates have been demonstrated as a viable imaging technology in a variety of systems, absolute flux measurements are nearly impossible to come by in the literature. Measurement of flux with hyperpolarized agents in an absolute sense depends upon the correct modeling of a variety of factors including delivery, T_1, effects of pulsing, and finally the enzymatic reactions themselves. Bayesian probability theory provides a method for modeling the signal time course following a bolus injection. Here Bayesian probability theory is used to infer the *delivery rate constant* for a bolus of HP tracer co-injected with a standard [1-^{13}C]pyruvate injection. The Bayesian calculations, implemented using Markov chain Monte Carlo with simulated annealing, result in samples drawn from the posterior probability for each parameter. For symmetric probability density functions, the mean and standard deviation of these samples are a natural measure of the parameter and the uncertainty in the estimation.

Methods

Rat hearts were excised under a protocol approved by the institutional animal care and use committee. The excised hearts were immediately reperfused in Langendorff mode with Krebs-Henseleit (KH) bicarbonate buffer bubbled with a 95/5 mixture of O_2/CO_2 and a substrate consisting of 2 mM pyruvate. The perfused heart was placed inside a Varian VNMRS 9.4 T spectrometer equipped with a Doty 25 mm broadband detection probe. Sodium [1-^{13}C]pyruvate was dissolved in a 50/50 mixture of H_2O/[^{13}C]DMSO. The labeled DMSO served as an internal standard for measuring the delivery of the solution without being subject to degradation/metabolism. 4 ml of H_2O was used to dissolve the hyperpolarized sample, of which 3 ml was subsequently diluted to produce 23 ml of 2 mM [1-^{13}C]pyruvate for injection. The solution was injected by catheter over ~ 60 seconds, with detection of the signal every 5 seconds using a 66 degree ^{13}C inspection pulse. The equation used to model the hyperpolarized signal was based upon a standard bolus delivery model modified to include pulsing and T_1 effects, and is not shown here due to length.

Results

Figure 1 (left) shows the data in red, a model generated from the parameters that had maximum posterior probability in blue and the residuals, the difference between the data and the model, in green. The simulations converged to essentially identical answers regardless of the prior probabilities. Figure 1 (right) shows 3 models for the delivery of the

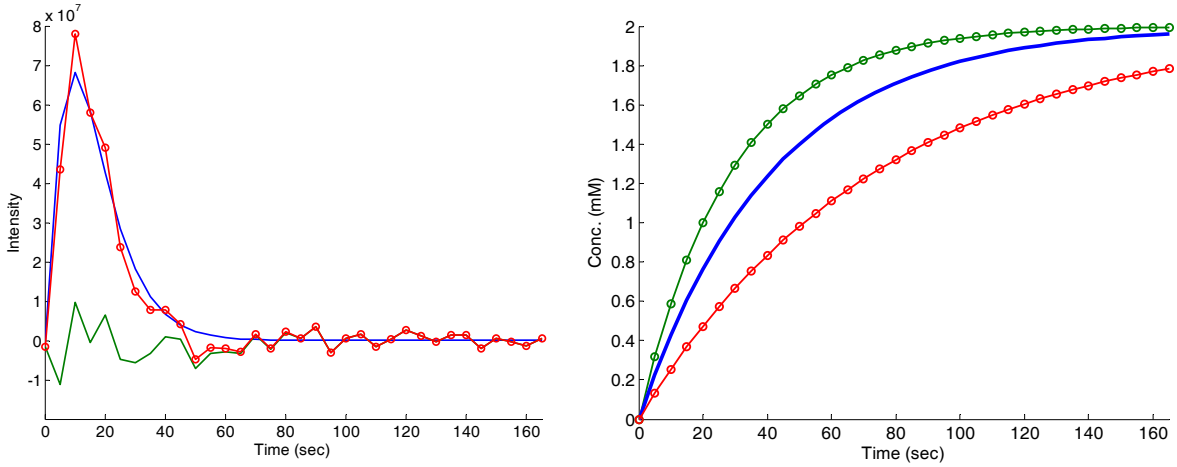

Figure 1. Time course of the hyperpolarized DMSO signal with the simulation and residual (left), and the predicted injection curves ± standard deviation.

hyperpolarized pyruvate to the perfused heart with the most likely answer (blue) flanked by curves at plus or minus the standard deviation of the injection rate as estimated by Bayesian probability theory.

Conclusions

These results show that Bayesian probability theory allows realistic models of bolus injection of hyperpolarized substrates to be predicted. A correct description of the delivery curve is a necessary precondition to quantitatively estimating flux through enzymatic reactions. Future work will use this model as a basis for estimating the kinetics of pyruvate metabolism in the perfused heart.