

Developing method to quantify tumour response to treatment using hyperpolarized ^{13}C magnetic resonance imaging



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Introduction

- Increasing need to **determine tumour response to treatment** quickly
- For tumours exhibiting the **Warburg effect**, ^{13}C magnetic resonance imaging can be used to image metabolic activity in vivo
- Dissolution Dynamic Nuclear Polarization of $[1-^{13}\text{C}]$ pyruvate enhances the signal 10'000-fold [1]
→ Imaging **tissue distribution** of the metabolites in vivo is possible in real-time
- Compare **reaction kinetic constant k_{PL}** of pyruvate to lactate before and after treatment

Methods

- Implant COLO 205 tumour cells subcutaneously into mouse
- Image:**
 - Inject hyperpolarized ^{13}C -pyruvate
 - Acquire images with spectrally, spatially and temporally selective radiofrequency pulses for $[1-^{13}\text{C}]$ pyruvate and $[1-^{13}\text{C}]$ lactate
- Treat** mouse with etoposide (chemotherapeutic drug damaging DNA)
- Repeat imaging**
- Compare** pre- and post-treatment to see whether drug was effective (leading to a decrease in lactate production)

Model

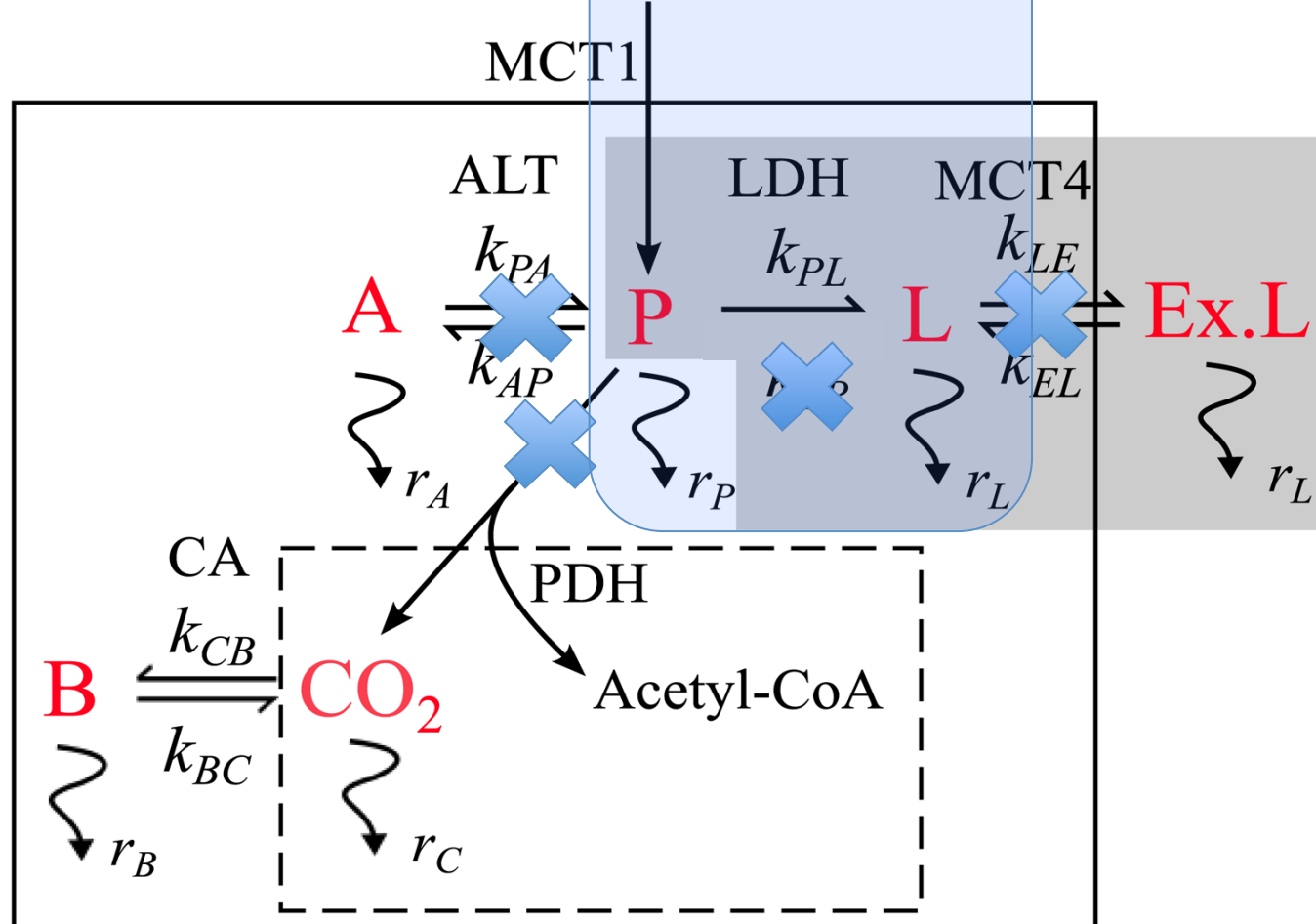


Fig. 1. Schematic diagram of metabolic pathway of injected hyperpolarized pyruvate
 P_{in} is the injected pyruvate, P is intracellular pyruvate, L and Ex.L are intra- and extracellular lactate, A is alanine, B is bicarbonate. Solid lines correspond to cell membrane, dashed lines to mitochondrial membrane. r_p and r_l are effective relaxing times of the hyperpolarized signal, where $r_i = 1/T_i - 1/TR \ln(\cos(\alpha_i))$, where T_i is cross-relaxation time of metabolite i, TR is the time between two consecutive pulses and α_i is the flip-angle for the radio frequency pulse exciting metabolite i. Crossed arrows are neglected. The reduced model is highlighted in blue.

Assumptions

- Neglect pyruvate flux into alanine and citric cycle
- Neglect flux of lactate into pyruvate
- No distinction between intra- and extracellular lactate pool
- k_{PL} is measure of tumour metabolic activity**
- End up with **modified Bloch equations**:

$$\frac{dP}{dt} = -r_p P - k_{PL} P + AIF^* \quad \text{and} \quad \frac{dL}{dt} = -r_l L + k_{PL} P$$

*AIF is Arterial Input Function (quantifying how injected pyruvate arrives to the tumour through the bloodstream)

Noise

- The measured data obeys **Rician** distribution with parameters corresponding to signal and background noise
- Difficult to estimate signal for low signal-to-noise ratio (SNR) due to bias
→ need to correct for this

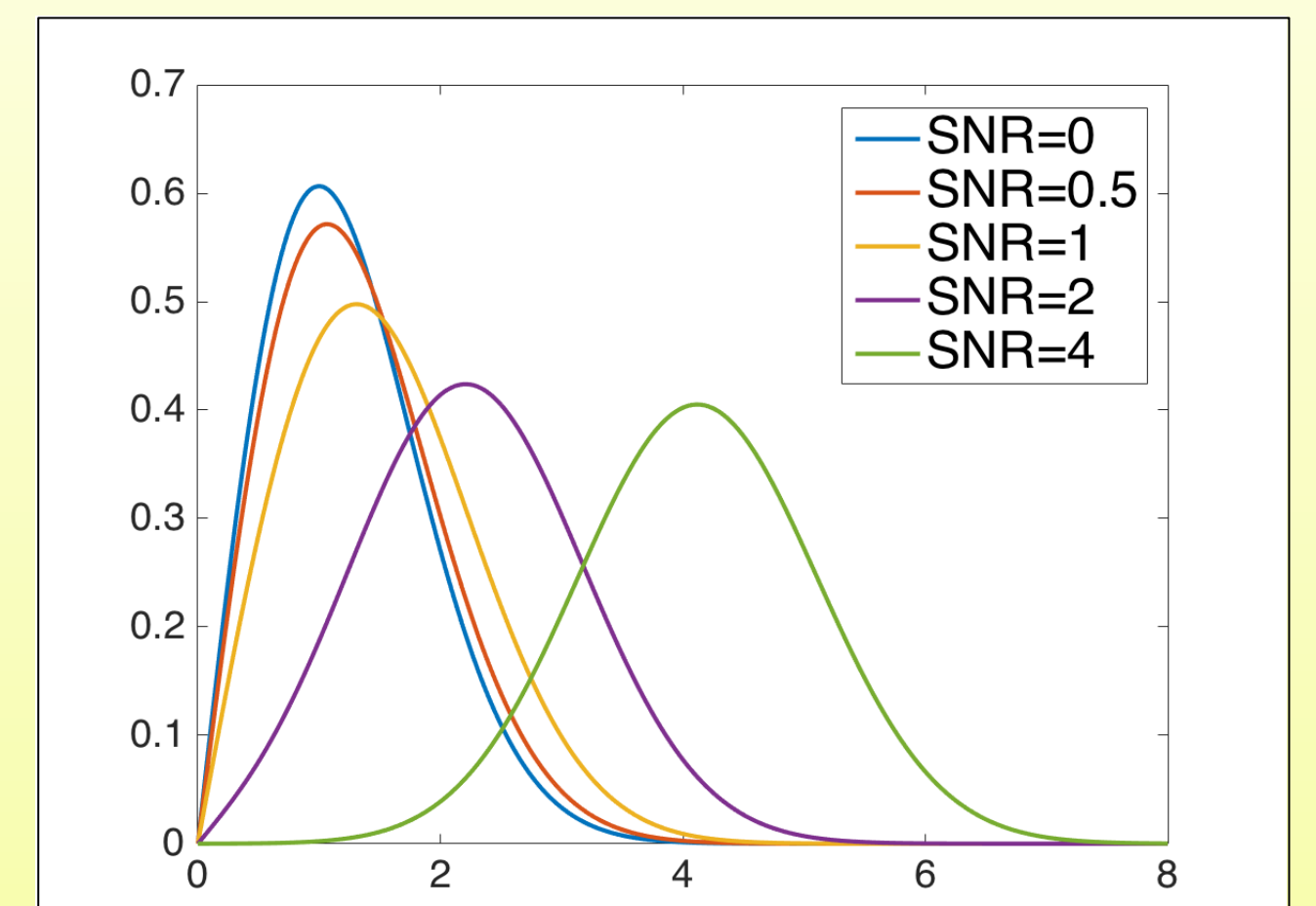


Fig. 2. Rician distribution with fixed background noise and varying signal-to-noise-ratio (SNR).

How to calculate k_{PL} ?

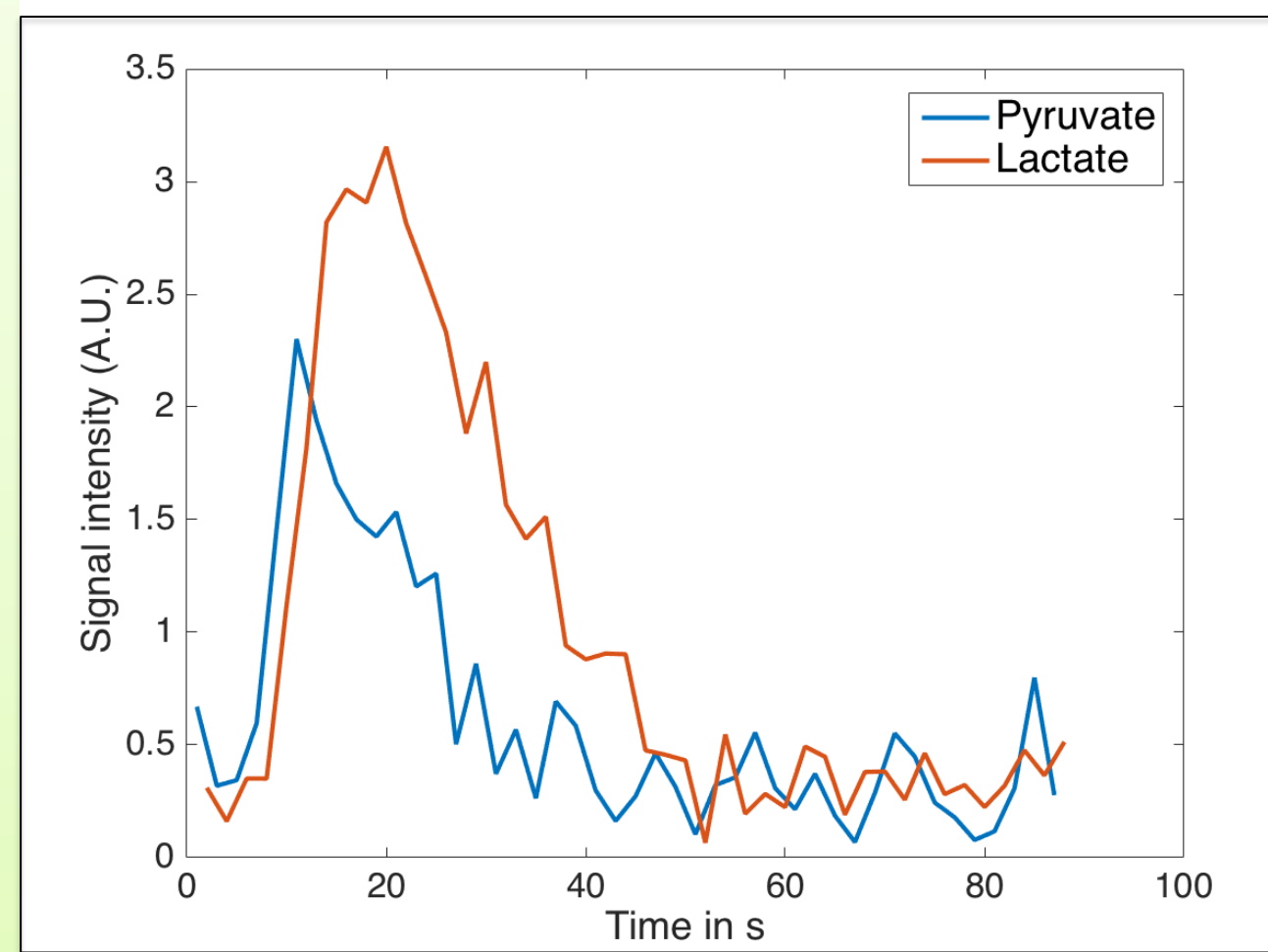
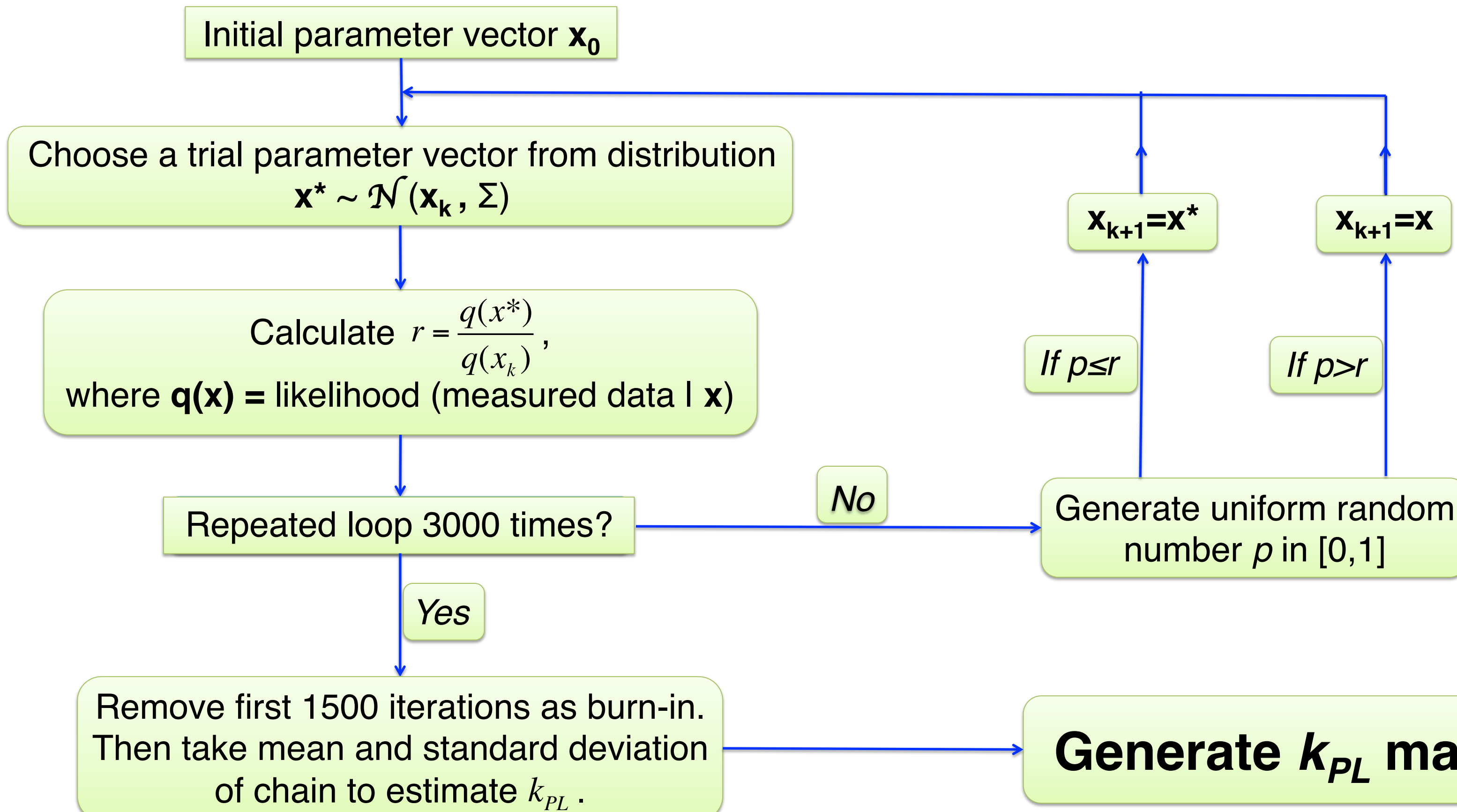


Fig. 3. Time-courses of ^{13}C -labeled pyruvate and lactate in sample pixel

Markov Chain Monte Carlo fitting^[2] of parameters (k_{PL} , r_L , AIF)



Area-under-curve estimation^[3]

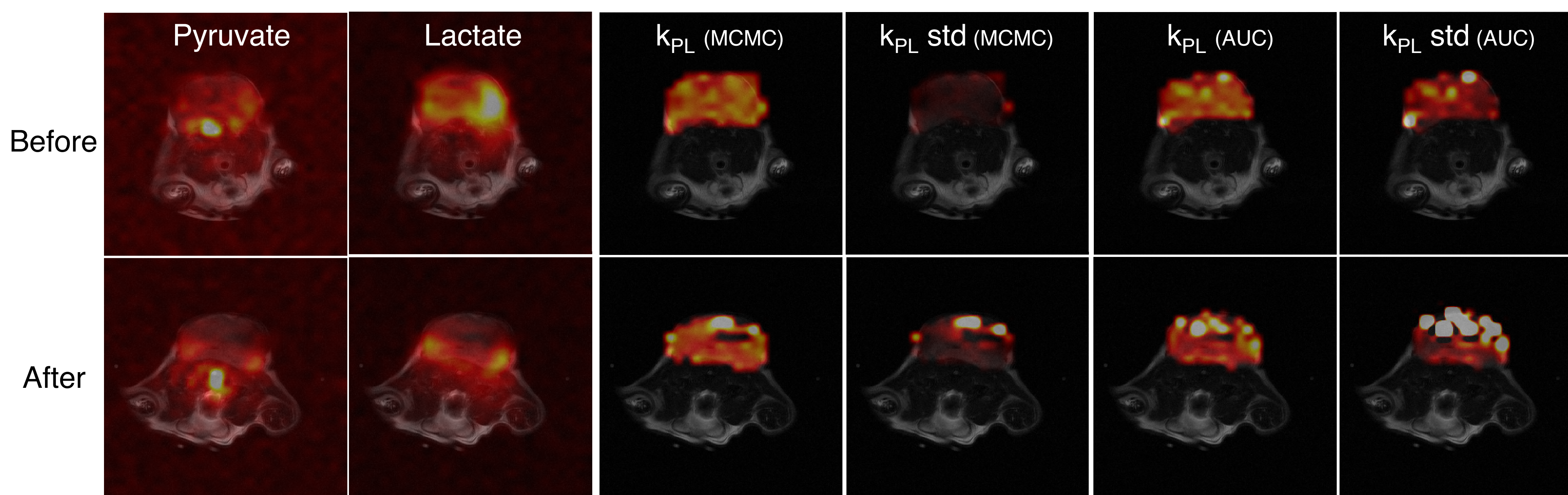
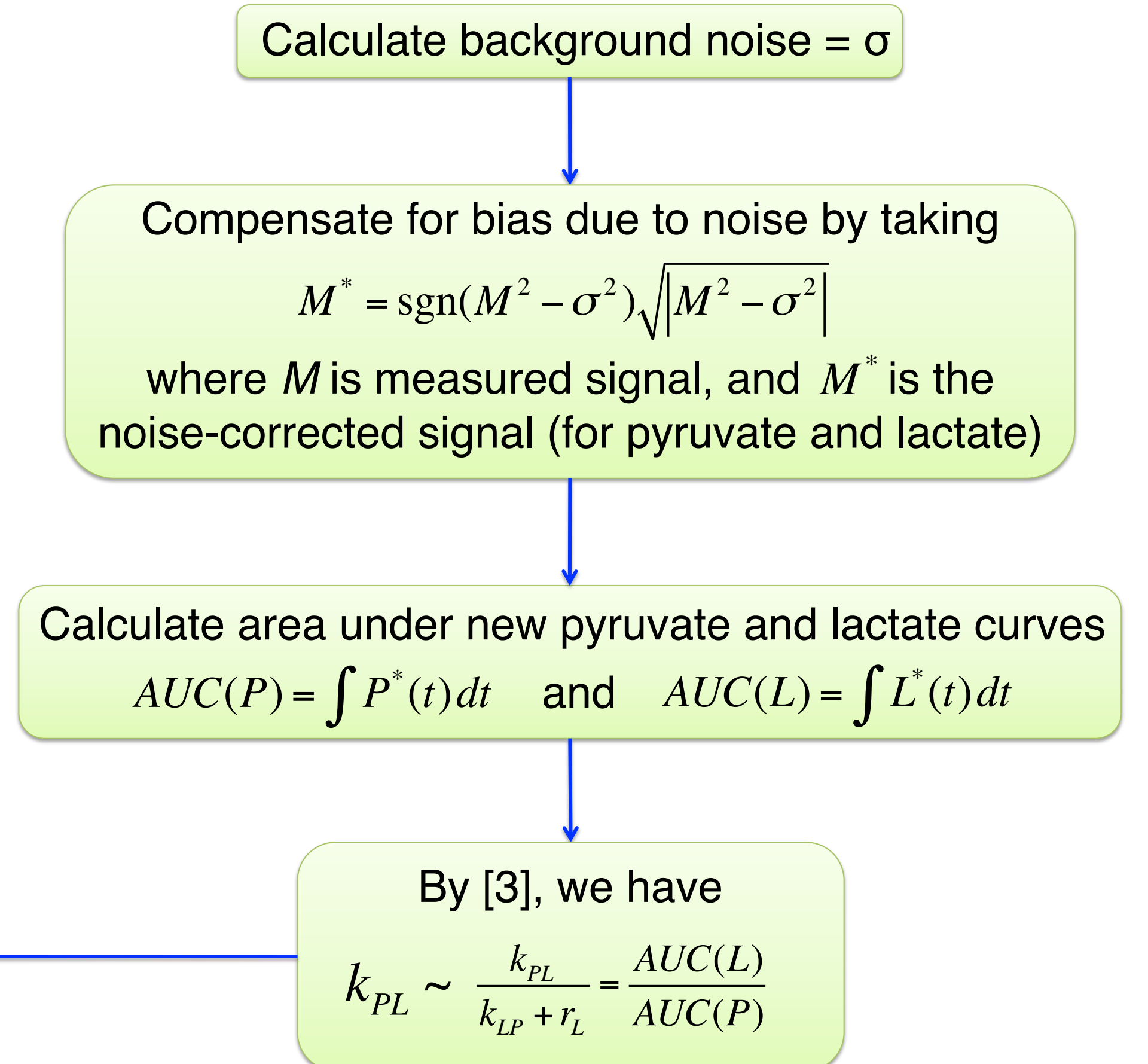


Fig. 4. Comparison of k_{PL} values before and after etoposide treatment in a COLO 205 tumour bearing mouse. In addition, we compare the MCMC and AUC methods described above. Pyruvate and lactate maps are the measured values of pyruvate and lactate summed over the time interval 1-15s (pyruvate) and 5-15s (lactate), on the same scale. Standard deviation (std) maps are estimates of the standard deviation of k_{PL} ; the value of two standard deviations is shown. k_{PL} maps have range 0 to 0.2 s⁻¹, while k_{PL} std maps have range 0 to 0.02 s⁻¹. AUC maps have range 0 to 1 (AUC ratio), and AUC std estimates have range 0 to 0.4 (AUC ratio). The k_{PL} maps of the two methods show closer resemblance than what the standard deviation maps predicts, hence the std estimates for the AUC method are very high.

Conclusions

- k_{PL} values decreased after treatment**
 - cell death was confirmed by post mortem histology
- Intratumour metabolic heterogeneity stems mostly from differences in perfusion
- Markov Chain Monte Carlo (MCMC)**
 - ✓ Reliable
 - ✓ Tight error bounds
 - ❖ Slow
 - ❖ Doesn't work with low SNR
- Area-under-curve**
 - ✓ Fast
 - ✓ Works for low SNR as well
 - ❖ Wide error bounds

→ Use the two methods combined to get optimal forecast

[1]. Day, SE et al. (2007): Detecting tumor response to treatment using hyperpolarized ^{13}C magnetic resonance imaging and spectroscopy, *Nature Medicine* 2007 Nov;13(11):1382-7

[2]. Kuchel, PW et al. (2011): Relaxation times of spin states of all ranks and orders of quadrupolar nuclei estimated from NMR z-spectra: Markov chain Monte Carlo analysis applied to $^{7}\text{Li}^+$ and $^{23}\text{Na}^+$ in stretched hydrogels. *J Magn Reson* 212 (2011) 40-46

[3]. Hill, DK et al. (2013): Model Free Approach to Kinetic Analysis of Real-Time Hyperpolarized ^{13}C Magnetic Resonance Spectroscopy Data, *Plos One* 2013 Sep 4;8(9):e71996.