Purpose
Recent studies on hyperpolarized ^{13}C-pyruvate metabolism performed on mice[1] and prostate cancer patients[2] showed that pyruvate to lactate conversion rate can differentiate normal from malignant tissue. Estimation of metabolic kinetics is based on compartmental modelling of dynamic data, and depends on the accurate measurement/estimation of the pyruvate input function (PIF). When PIF measurements from the arterial blood are not available, the PIF is usually modelled using a box-car function[1] or a model-free formulism[3] based on the ratio of total areas under the curve (AUC) of the injected and product metabolite. This work examines the effect of modelling the PIF as a Gaussian function, which partially accounts for the time pyruvate needs to travel and dispersion effects.

Theory
Hyperpolarized ^{13}C-pyruvate MRS imaging provides metabolic information within very short time, including relaxation ratios and enzymatically driven conversion to pyruvate metabolites. Recently developed acquisitions substantially improved the temporal resolution allowing for kinetic modelling. To model the chemical exchanges a semi-classical description with the modified Bloch-McConnell equations is used.

$$\frac{\text{d}P}{\text{d}t}=-k_{P\rightarrow X}P(t)-r_{P}P(t)+k_{X\rightarrow P}X(t)$$
$$\frac{\text{d}X}{\text{d}t}=-k_{X\rightarrow P}X(t)-r_{X}X(t)+k_{P\rightarrow X}P(t)$$
Where $k_{P\rightarrow X}$, $k_{X\rightarrow P}$ are the forward and back conversion of pyruvate (P) to its metabolic products (X), $r_X=1/T1_X + (1-\cos\theta)^{1/TR}$, $T1_X$ is the relaxation rate of each metabolite, TR is the repetition time and θ is the flip angle. We will make the assumption $k_{X\rightarrow P}\sim 0$. The PIF can be modelled with a box-car function, based on the rate (a.u sec^{-1}) and the duration (sec) of injection. The proposed method uses a Gaussian model $PIF\sim f_1 * normal(f_2/2, f_2)$, where f_1, f_2 are free parameters representing the height and the shape of the peak respectively. A more complex function would be able to delineate PIF better, but it would require the fitting of more free parameters. Alternatively a model-free formulism can be used which approximates the kinetics using the ratios of AUC of the injected and product metabolites,
$$\frac{AUC(X)}{AUC(P)}\approx\frac{k_{P\rightarrow X}}{r_{X}}$$

Methods
10 canine cancer patients with biopsy-verified spontaneous malignant tumors underwent dynamic nuclear polarization (DNP) with ^{13}C-pyruvate MRS imaging on a combined PET/MR clinical scanner (Siemens mMR Biograph, Siemens, Germany). This set of experiments was earlier reported in [4]. An axial-oblique 40 mm thick slab covering the tumor region, dynamic ^{13}C-pyruvate MRS was performed. Parameters were TR=1,000 ms, echo time TE=0.757 ms, θ=5°, bandwidth 4,000 Hz. The acquisition was repeated 180 times, commencing at the injection of the hyperpolarized ^{13}C-pyruvate (23 mL). Peak heights of ^{13}C-pyruvate, ^{13}C-lactate, and ^{13}C-alanine were quantified using AMARES provided in the jMRUI package. AMARES is a time domain fitting technique used in spectroscopy that allows the user to provide prior information about the spectrum. The maximum peak was assigned to pyruvate (usually ~171 ppm), whereas the other metabolites were assigned the following frequency shifts to pyruvate: 12.12 ppm (lactate), and 5.52 ppm (alanine). Linewidths and other constraints were adjusted to minimize the residual error in AMARES. Peak heights modelled with the modified Bloch-McConnell equations as a function of time were fitted using the simplex algorithm. The proposed Gaussian PIF was evaluated in terms of goodness-of-fit using the Kolmogorov-Smirnov (KS) test and its agreement with the model-free formalism.

Results
Figure 1 illustrates that the proposed Gaussian PIF lead to a better goodness-of-fit compared to the box-car PIF. The improvement was significantly better (following Mann–Whitney U test) for the lactate (p=0.011) and alanine (p=0.0004) fits. Figure 2 shows an example of a box-car and a Gaussian PIF, as well as a fitting example of the dynamic metabolite peaks using the 2-compartmental model with a Gaussian PIF. Figure 3 illustrates a box-plot of the estimated $k_{P\rightarrow X}/r_X$ with the model-free formalism and the compartmental modelling using the box-car and the Gaussian PIF. Following Mann–Whitney U test, when a Gaussian PIF was used the estimated $k_{P\rightarrow X}/r_X$ were not different from the ones estimated from model-free formalism (p= 0.495 lactate, and p =0.1 alanine), whereas for a box-car PIF they were significantly different (p= 0.003 lactate, and p =0.002 alanine).

Conclusions
The suggested Gaussian PIF significantly improved the fitting of the model to the dynamic curves of metabolites compared to the commonly used box-car PIF. Kinetic modelling using a Gaussian PIF was in agreement with the model-free formalism while providing more information about the rates of conversion, $k_{P\rightarrow X}$ and relaxation rates, r_X.

Acknowledgements
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References
[1] ML Zierhut et al, Journal of Magnetic Resonance 2010; 202: 85–92. [2] SJ Nelson et al, Sci Transl Med. 2013;5(198):198. [3] DK Hill et al, PLoS One. 2013; 8(9): 71996. [4] H. Gutte et al., J Nucl Med. 2015 Sep 3. [Epub ahead of print]]

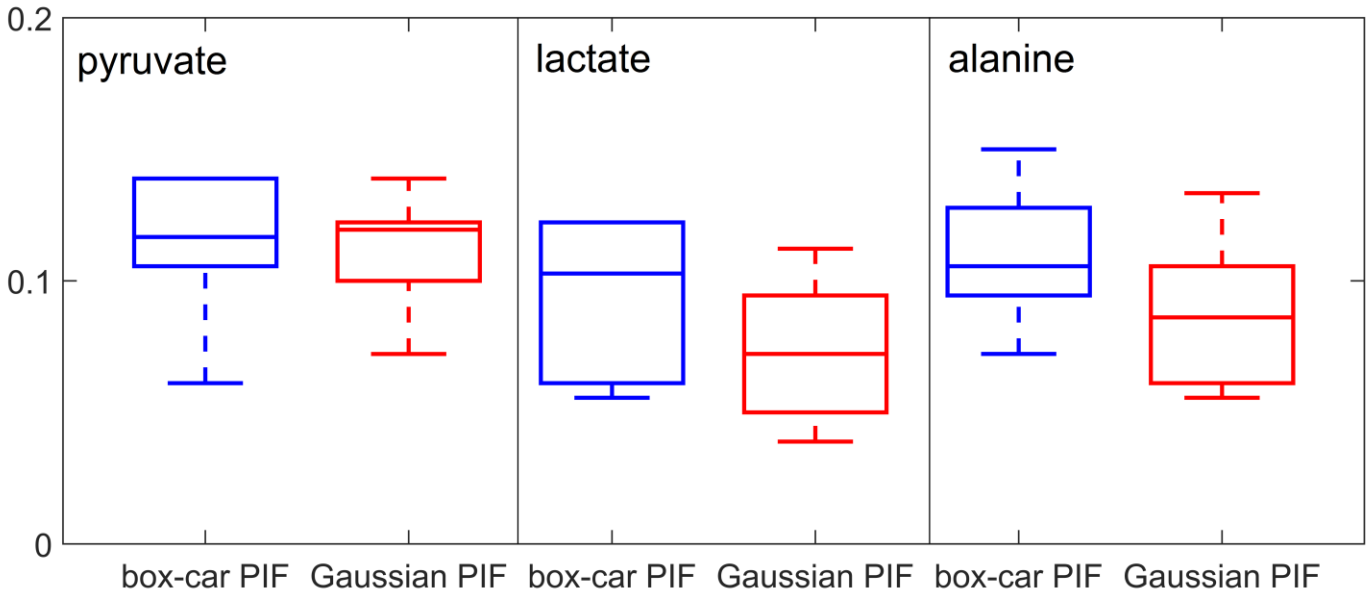

Figure 1: Kolmogorov-Smirnov (KS) statistic test across the 10 canine dynamic peak heights for the compartmental model using either the box car or the Gaussian pyruvate input function (PIF).

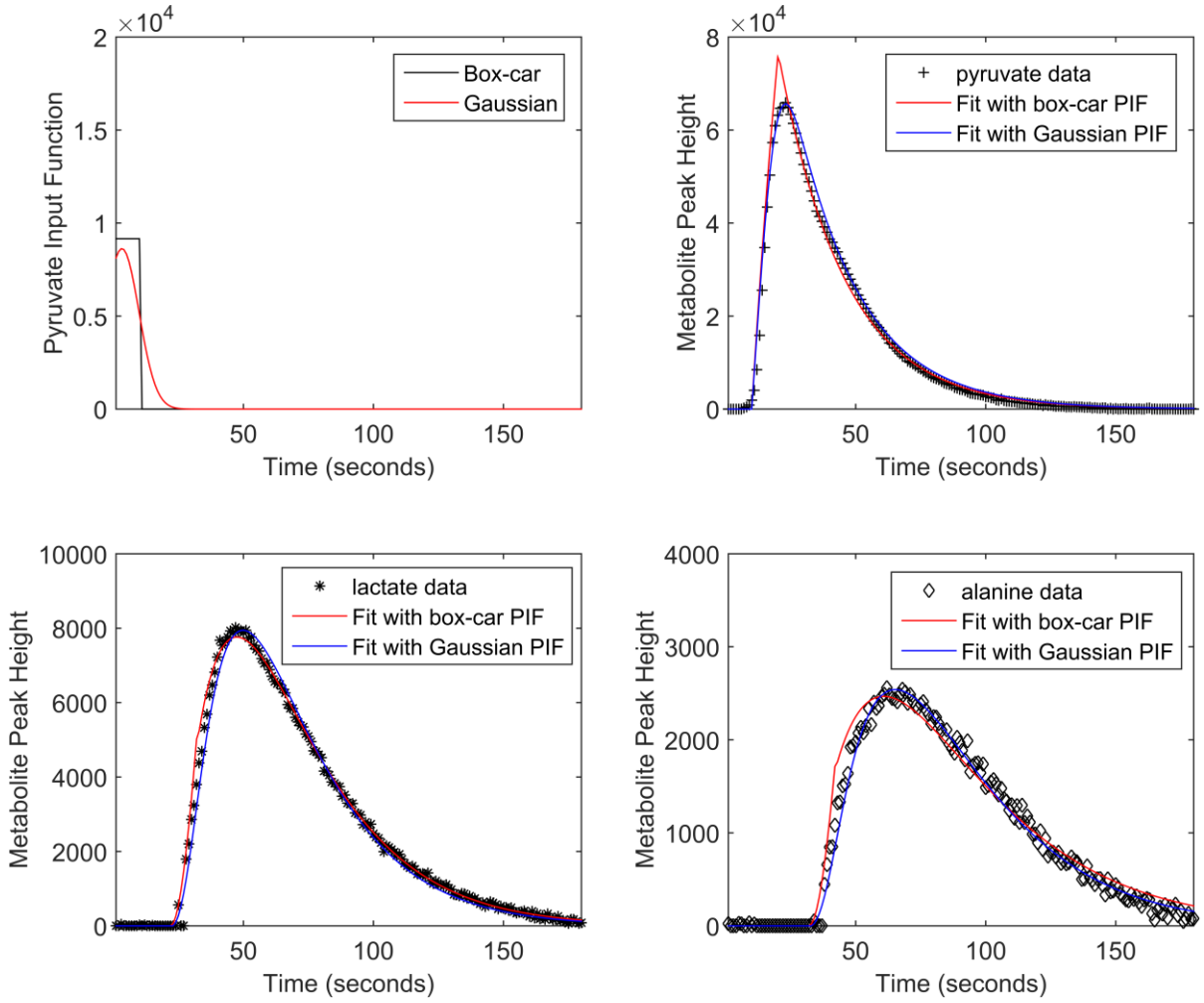

Figure 2: Examples of box-car and Gauss PIF, and dynamic curves of the metabolite peaks and the modelled best fit lines using a Gaussian PIF.

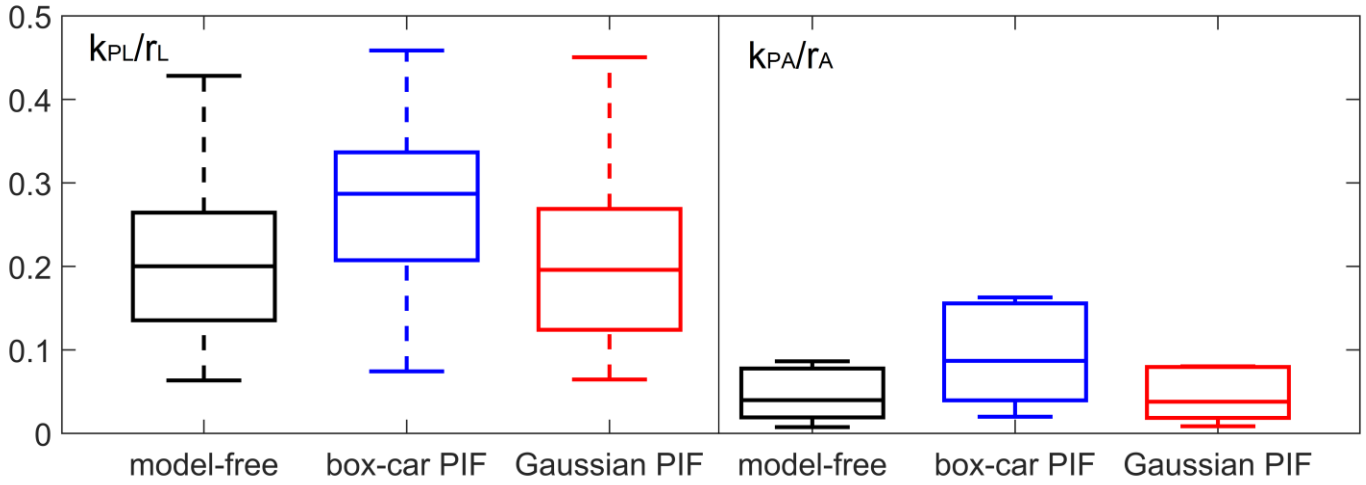

Figure 3: Estimated $k_{P\rightarrow X}/r_X$ across the 10 canine dynamic peak heights using the model-free formalism and the compartmental model using either the box car or the Gaussian pyruvate input function (PIF).