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Models for plasma metabolite correction

Models for describing the fraction of labeled metabolites in plasma are developed mainly to 1) remove noise in the measured fractions, 2) to allow interpolation of the fraction between the few metabolite samples, 3) to allow extrapolation of the fraction in cases where metabolite fraction can no longer be determined because of low activity counts, and 4) to allow the application of population based average metabolite correction. This document reviews the models that are used to correct the plasma time-activity curves (TACs) for labeled metabolites in PET measurements.

Mathematical function fitting

Exponential functions

A common approach is to fit an exponential or polynomial function to extend the small number of assayed metabolite fractions [Hawkins et al 1989]. In Abi-Dargham's implementation [Abi-Dargham et al 1999] the smaller exponential of two exponential function was constrained to the difference between the terminal washout rate of cerebellar (reference region) activity and the smallest elimination rate constant of the total plasma activity.

Tracer is injected intravenously for a defined duration of time, which often leads into unhanged percentage of parent tracer fraction during the first one or two minutes. One solution is to assume that fraction is 1 during a specified inital period, e.g. 3 min after injection, and then decreases exponentially or biexponentially; this approach has been suggested to [^{11}C]flumazenil studies [Magata et al. 2003].

Hill-type function

A "Hill" type function (Eq. 1 for the metabolite fraction) was presented for [*carbonyl*-^{11}C]WAY-100635 studies [Gunn et al 1998]. It has been applied to other tracers also in our centre, e.g. [^{11}C]choline and [^{11}C]FLB. Examples of curves are shown in Fig. 1.

$$f_{Met} = \frac{\alpha \times t^{\beta}}{t^{\beta} + \gamma} \qquad (1)$$

This function has also been used in a simplified form for [^{11}C]carfentanil with assumption $\beta=1$ [Endres et al. 2003].

Watabe's empirical equation

For fitting the fractions of authentic tracer [^{11}C]MDL 100,907, a function (Eq. 2) was presented by Watabe et al. (2000). Examples of curves are shown in Fig. 2.

$$f_{Auth} = \frac{1}{\left[1+(\alpha \times t)^2\right]^{\beta}} \qquad (2)$$

Kinetic models

Huang et al. (1991) introduced the basic theory for using the substrate-product relationship between the authentic (parent) tracer and its labelled metabolites in plasma to replace the function fitting procedure. The modelling approach is suggested to give more reasonable results, at least as compared to the exponential fit [Huang et al 1991; Lammertsma et al 1993]. The models presented by Huang et al (1991) do not explicitly show the transports for reversible metabolism or clearance of metabolites from the body, but account for these rates in the existing model parameters; these implications need need to be considered in the physiological interpretation of the parameter values. Some tracer-specific compartmental models for the separation of plasma metabolites have been proposed.

Models for [^{18}F]FDOPA

Huang et al. (1991a) presented a model (Fig. 3), where the main metabolite, [^{18}F]OMFD and the other metabolites (MET) of [^{18}F]FDOPA were given their own compartments. The model was applied to measured data with different doses of inhibitor carbidopa, and the fitted parameters behaved as expected. The same model can also be used for only one metabolite [Huang et al. 1991b], which can be applied in the usual cases with carbidopa premedication.

Similar formulation for one metabolite with no reversible extravascular compartment was presented by Reith et al. (1990), and graphical methods are also applied to solve the model parameters [Reith et al., 1990; Gjedde et al., 1991; Cumming et al., 1994]. The model was extended to cover up to three metabolites, and exponential equations were derived for yielding the concentration curves [Cumming et al., 1993]. In the first step, curve for parent tracer is predicted with two parameters, the sum of the individual rates of generation of each metabolite, and a single rate of elimination applied to all metabolites. Secondly, using the parent tracer curve, the individual metabolite curves and their individual generation and elimination constants are predicted [Cumming et al., 1993].

Plot of the radioactivity ratio of metabolites to parent tracer versus time has been shown to be linear in certain conditions and pllied to simplify the blood analysis [Chan et al., 1992].

Model for [^{11}C]raclopride by Carson et al.

The compartmental model is presented in Fig. 5. and is based on the model developed by Huang et al. (1991), although the structure of the model is different. The metabolite term is calculated from a convolution formula, which was given with only three parameters:

$$C_{met}(t) = A\left(e^{-\lambda_1 t} - e^{-\lambda_2 t}\right) \otimes C_{tot}(t) \qquad (3)$$

and the model was reduced further by setting $k_4=0$, i.e. setting $A=\lambda_1\lambda_2/(\lambda_2-\lambda_1)$ [Carson et al., 1997].

Model by Lammertsma et al.

Lammertsma et al (1993) mentioned a "parallel multicompartment model" for [^{11}C]raclopride and also [^{11}C]deprenyl, but did no describe the model precisely. They determined the required number of compartments by "standard statistical tests".

Models for [^{15}O]O_2

Huang et al (1991) presented the model for modelling the blood (labelled water and oxygen) and plasma (labelled water) curves measured in [^{15}O]O_2 PET studies (Fig. 4). Iida et al (1993) excluded the tissue compartment in their own very simple model designed and validated for steady-state studies.

References

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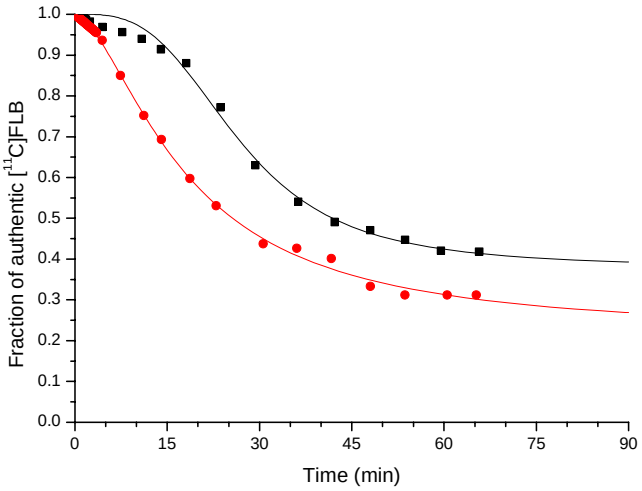

Fig. 1. Two examples of "Hill" type function fitted to measured fractions of authentic tracer in plasma.

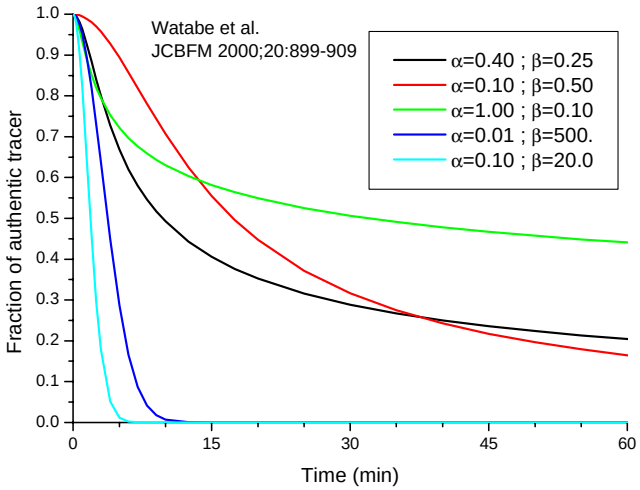

Fig. 2. Examples of functions from the equation suggested by Watabe et al. (2000).

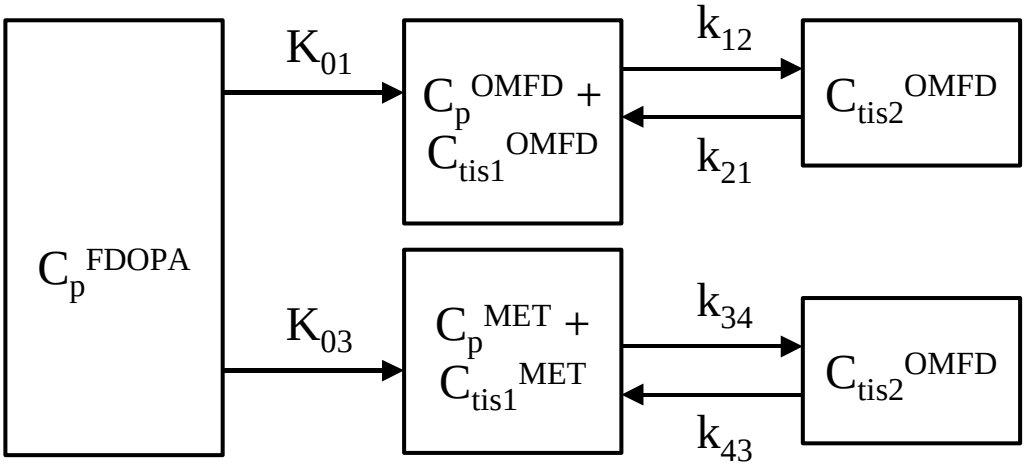

Fig. 3. Compartmental model for [^{18}F]FDOPA plasma metabolites [Huang et al 1991].

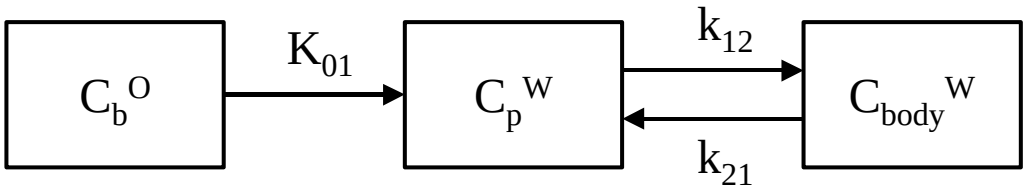

Fig. 4. Compartmental model for [^{15}O]O_2 blood metabolism [Huang et al 1991]. C_b^O represents the concentration of labelled oxygen in arterial blood, C_p^W the concentration of labelled water in plasma, which exchanges with labelled water in body, C_{body}^W.

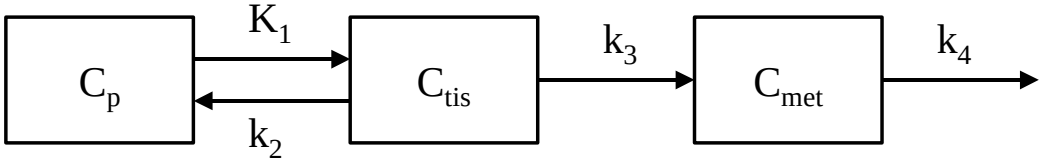

Fig. 5. Model used by Carson et al (1997) for analysis of [^{11}C]raclopride plasma metabolite data. [^{11}C]Raclopride in plasma (C_p) exchanges with raclopride in the body pool (C_{tis}) from which metabolites in plasma (C_{met}) are produced. The model was further reduced by assuming k_4=0 [Carson et al. 1997].