Turku PET Centre Modelling report TPCMOD0009 Appendix C
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New model for plasma metabolites

This document describes the mathematical equations required for simulation of a novel compartmental model for plasma metabolites (Fig. 1). The ODEs are solved using the second order Adams-Moulton method with trapezoidal rule (Kuwabara et al. 1993).

Compartmental model

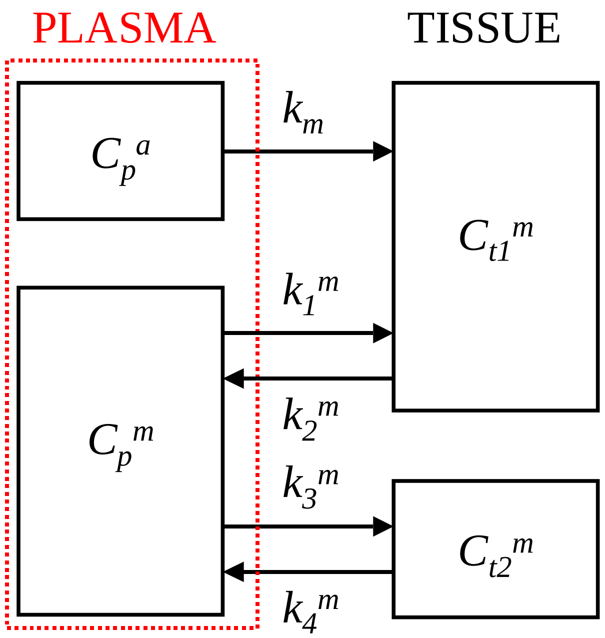

Figure 1. Compartment model for PET tracers with one labelled metabolite. For some tracers, it can be assumed that $k_1{}^m=0$ and/or that $k_4{}^m=0$. In some very specific cases the second tissue compartment may be excluded ("simple model"; $k_3{}^m= k_4{}^m 0$).

In PET studies, the total radioactivity concentration is measured. It equals the sum of labelled metabolite and parent (authentic) tracer concentration, which can be obtained as

$$C_p^a(t) = C_p^T(t) - C_p^m(t) \tag{1}$$

Differential equations

For the following compartments, the differential equations can be constructed from the model (Fig. 1):

$$\frac{dC_{t1}^m(t)}{dt} = k_m C_p^a(t) + k_1^m C_p^m(t) - k_2^m C_{t1}^m(t) \tag{2}$$

$$\frac{dC_p^m(t)}{dt} = k_2^m C_{t1}^m(t) + k_4^m C_{t2}^m(t) - \left(k_1^m + k_3^m\right) C_p^m(t) \tag{3}$$

$$\frac{dC_{t2}^m(t)}{dt} = k_3^m C_p^m(t) - k_4^m C_{t2}^m(t) \tag{4}$$

Integration of Eq. (4), and solving using the second order Adams-Moulton method with trapezoidal rule (concentrations at time point 0 are assumed to be 0) gives equations for the concentration of metabolite in the second tissue compartment, and its integral:

$$C_{t2}^m(T) = \frac{k_3^m \int_0^T C_p^m(t)dt - k_4^m \left[\int_0^{T-\Delta t} C_{t2}^m(t)dt + \frac{\Delta t}{2} C_{t2}^m(T-\Delta t) \right]}{1 + \frac{\Delta t}{2} k_4^m} \tag{5}$$

$$\int_0^T C_{t2}^m(t)dt = \frac{k_3^m \frac{\Delta t}{2}}{1 + \frac{\Delta t}{2} k_4^m} \int_0^T C_p^m(t)dt + \frac{\left[\int_0^{T-\Delta t} C_{t2}^m(t)dt + \frac{\Delta t}{2} C_{t2}^m(T-\Delta t) \right]}{1 + \frac{\Delta t}{2} k_4^m} \tag{6}$$

Integration of Eq. (3), substitution of Eq. (6), and solving using the second order Adams-Moulton method with trapezoidal rule gives equations for the concentrations of metabolites in plasma compartment and its integral:

$$C_p^m(T) = \frac{\left\{ \begin{array}{c} k_2^m \int_0^T C_{t1}^m(t)dt + A \left[\int_0^{T-\Delta t} C_{t2}^m(t)dt + \frac{\Delta t}{2} C_{t2}^m(T-\Delta t) \right] \\ -\left(k_1^m + k_3^m - k_3^m \frac{\Delta t}{2} A\right) \left[\int_0^{T-\Delta t} C_p^m(t)dt + \frac{\Delta t}{2} C_p^m(T-\Delta t) \right] \end{array} \right\}}{1 + \frac{\Delta t}{2}\left(k_1^m + k_3^m - k_3^m \frac{\Delta t}{2} A\right)} \tag{7}$$

$$\int_0^T C_p^m(t)dt = \frac{\left\{ \begin{array}{c} k_2^m \frac{\Delta t}{2} \int_0^T C_{t1}^m(t)dt + A \frac{\Delta t}{2} \left[\int_0^{T-\Delta t} C_{t2}^m(t)dt + \frac{\Delta t}{2} C_{t2}^m(T-\Delta t) \right] \\ + \left[\int_0^{T-\Delta t} C_p^m(t)dt + \frac{\Delta t}{2} C_p^m(T-\Delta t) \right] \end{array} \right\}}{1 + \frac{\Delta t}{2}\left(k_1^m + k_3^m - k_3^m \frac{\Delta t}{2} A\right)} \tag{8}$$

, where $A=k_4^m/(1+k_4^m\Delta t/2)$.

Substitution of Eq. (1) into Eq. (2), integration, substitution of Eq. (8), and similar solving as before gives the equation for the concentration of metabolite in the first tissue compartment:

$$C_{t1}^{m}(T)=\frac{\left\{\begin{aligned}&k_m\int_0^T C_p^T(t)dt-k_2^m\left(1-\tfrac{\Delta t}{2}B\right)\left[\int_0^{T-\Delta t}C_{t1}^m(t)dt+\tfrac{\Delta t}{2}C_{t1}^m(T-\Delta t)\right]\\&+B\left[\int_0^{T-\Delta t}C_p^m(t)dt+\tfrac{\Delta t}{2}C_p^m(T-\Delta t)\right]+AB\tfrac{\Delta t}{2}\left[\int_0^{T-\Delta t}C_{t2}^m(t)dt+\tfrac{\Delta t}{2}C_{t2}^m(T-\Delta t)\right]\end{aligned}\right\}}{1+\tfrac{\Delta t}{2}k_2^m\left(1-\tfrac{\Delta t}{2}B\right)} \qquad (9)$$

, where $B=(k_1^m-k_m)/[1+(\Delta t/2)(k_1^m+k_3^m-k_3^m A\Delta t/2)]$.

Differential equations for the simple model

When the second compartment for the metabolite is excluded from the model ($k_3^m=k_4^m=0$; Fig. 2), the differential equations reduce to:

$$\frac{dC_t^m(t)}{dt}=k_m C_p^a(t)+k_1^m C_p^m(t)-k_2^m C_t^m(t) \qquad (10)$$

$$\frac{dC_p^m(t)}{dt}=k_2^m C_t^m(t)-k_1^m C_p^m(t) \qquad (11)$$

Note that this simple model can not be applied to most tracers; usually k_3^m needs to be included, and model is then already very simple since concentration in the second tissue compartment does not need to be calculated.

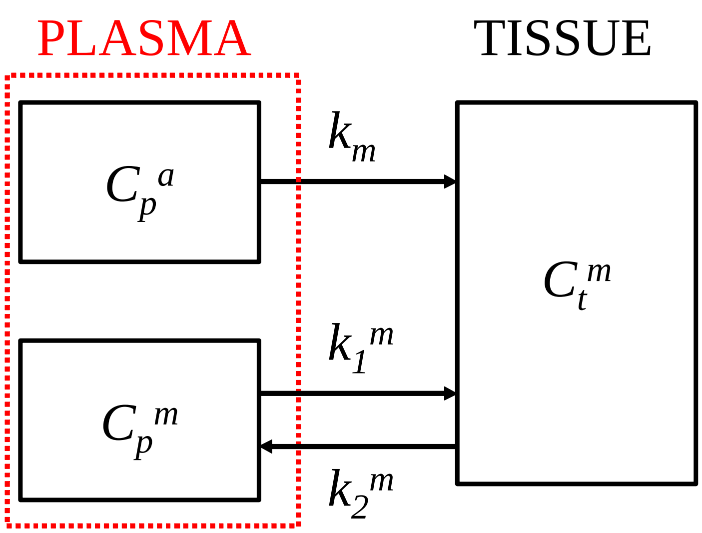

Figure 2. Simple compartment model for PET tracers with one labelled metabolite. For some tracers, it can be assumed that k_1^m=0.

Integration of Eq. (11), and solving using the second order Adams-Moulton method with trapezoidal rule gives equations for the concentrations of metabolites in plasma compartment and its integral:

$$C_p^m(T) = \frac{\left\{ \begin{array}{c} k_2^m \int_0^T C_t^m(t)dt \\ -k_1^m \left[\int_0^{T-\Delta t} C_p^m(t)dt + \frac{\Delta t}{2} C_p^m(T-\Delta t) \right] \end{array} \right\}}{1 + \frac{\Delta t}{2} k_1^m} \qquad (12)$$

$$\int_0^T C_p^m(t)dt = \frac{\left\{ \begin{array}{c} k_2^m \frac{\Delta t}{2} \int_0^T C_t^m(t)dt + \\ + \left[\int_0^{T-\Delta t} C_p^m(t)dt + \frac{\Delta t}{2} C_p^m(T-\Delta t) \right] \end{array} \right\}}{1 + \frac{\Delta t}{2} k_1^m} \qquad (13)$$

Substitution of Eq. (1) into Eq. (10), integration, substitution of Eq. (11), and similar solving as before gives the equation for the concentration of metabolite in the tissue compartment:

$$C_t^m(T) = \frac{\left\{ \begin{array}{l} k_m \int_0^T C_p^T(t)dt - k_2^m \left(1 - \frac{\Delta t}{2} B\right) \left[\int_0^{T-\Delta t} C_t^m(t)dt + \frac{\Delta t}{2} C_t^m(T-\Delta t) \right] \\ + B \left[\int_0^{T-\Delta t} C_p^m(t)dt + \frac{\Delta t}{2} C_p^m(T-\Delta t) \right] \end{array} \right\}}{1 + \frac{\Delta t}{2} k_2^m \left(1 - \frac{\Delta t}{2} B\right)} \qquad (14)$$

, where $B=(k_1^m-k_m)/[1+(\Delta t/2)k_1^m]$.

References

1. Kuwabara H, Cumming P, Reith J, Léger G, Diksic M, Evans AC, Gjedde A. Human striatal L-DOPA decarboxylase activity estimated in vivo using 6-[^{18}F]fluoro-DOPA and positron emission tomography: error analysis and application to normal subjects. *J Cereb Blood Flow Metab* 1993; 13:43-56.