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Extended Carson's model for plasma metabolites

This document describes the mathematical equations required for simulation of one of the possible compartmental models for plasma metabolites proposed by Carson et al. (1997), and extended in this report. The ODEs are solved using the second order Adams-Moulton method with trapezoidal rule [Kuwabara et al. 1993].

Compartmental model

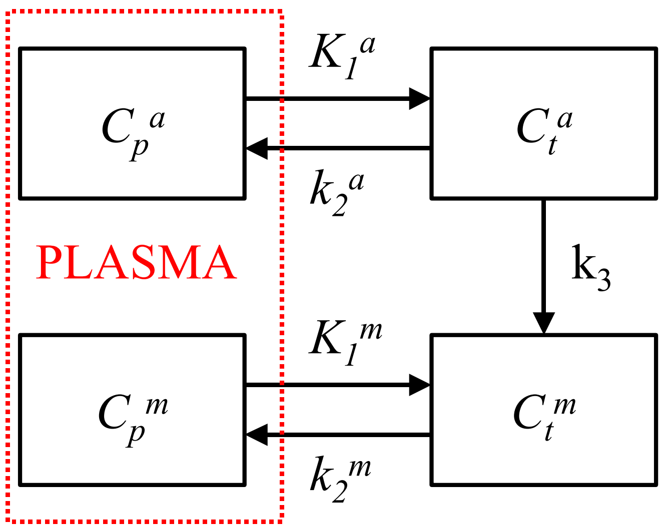

Fig. B1-1. Generalized compartment model for PET tracers with one labelled metabolite. This is similar to the model proposed by Carson et al. (1997) for [^{11}C]raclopride, if it is assumed that $K_1^m=0$.

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:

$$\frac{dC_t^a(t)}{dt} = K_1^a C_p^a(t) - \left(k_2^a + k_3\right) C_t^a(t) \tag{2}$$

$$\frac{dC_t^m(t)}{dt} = k_3\, C_t^a(t) - k_2^m\, C_t^m(t) + K_1^m C_p^m(t) \tag{3}$$

$$\frac{dC_p^m(t)}{dt} = -K_1^m C_p^m(t) + k_2^m\, C_t^m(t) \tag{4}$$

Integration of Eq. (3), 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 tissue, and its integral:

$$C_t^m(T) = \frac{k_3 \int_0^T C_t^a(t)dt + K_1^m \int_0^T C_p^m(t)dt - k_2^m \left[\int_0^{T-\Delta t} C_t^m(t)dt + \tfrac{\Delta t}{2} C_t^m(T-\Delta t) \right]}{1 + \tfrac{\Delta t}{2} k_2^m} \qquad (5)$$

$$\int_0^T C_t^m(t)dt = \frac{k_3 \tfrac{\Delta t}{2}}{1 + \tfrac{\Delta t}{2} k_2^m} \int_0^T C_t^a(t)dt + \frac{K_1^m \tfrac{\Delta t}{2}}{1 + \tfrac{\Delta t}{2} k_2^m} \int_0^T C_p^m(t)dt + \frac{\left[\int_0^{T-\Delta t} C_t^m(t)dt + \tfrac{\Delta t}{2} C_t^m(T-\Delta t) \right]}{1 + \tfrac{\Delta t}{2} k_2^m} \qquad (6)$$

Integration of Eq. (4), 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:

$$C_p^m(T) = \frac{\left[\begin{array}{c} k_3 \tfrac{\Delta t}{2} \dfrac{k_2^m}{1 + \tfrac{\Delta t}{2} k_2^m} \int_0^T C_t^a(t)dt \\ + \dfrac{k_2^m}{1 + \tfrac{\Delta t}{2} k_2^m} \left[\int_0^{T-\Delta t} C_t^m(t)dt + \tfrac{\Delta t}{2} C_t^m(T-\Delta t) \right] \\ - K_1^m \left(1 - \tfrac{\Delta t}{2} \dfrac{k_2^m}{1 + \tfrac{\Delta t}{2} k_2^m} \right) \left[\int_0^{T-\Delta t} C_p^m(t)dt + \tfrac{\Delta t}{2} C_p^m(T-\Delta t) \right] \end{array} \right]}{1 + \tfrac{\Delta t}{2} K_1^m \left(1 - \tfrac{\Delta t}{2} \dfrac{k_2^m}{1 + \tfrac{\Delta t}{2} k_2^m} \right)} \qquad (7)$$

$$\int_0^T C_p^m(t)dt = \frac{\left[\begin{array}{c} k_3 \left(\tfrac{\Delta t}{2}\right)^2 \dfrac{k_2^m}{1 + \tfrac{\Delta t}{2} k_2^m} \int_0^T C_t^a(t)dt \\ + \dfrac{k_2^m}{1 + \tfrac{\Delta t}{2} k_2^m} \tfrac{\Delta t}{2} \left[\int_0^{T-\Delta t} C_t^m(t)dt + \tfrac{\Delta t}{2} C_t^m(T-\Delta t) \right] \\ + \left[\int_0^{T-\Delta t} C_p^m(t)dt + \tfrac{\Delta t}{2} C_p^m(T-\Delta t) \right] \end{array} \right]}{1 + \tfrac{\Delta t}{2} K_1^m \left(1 - \tfrac{\Delta t}{2} \dfrac{k_2^m}{1 + \tfrac{\Delta t}{2} k_2^m} \right)} \qquad (8)$$

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

$$C_p^m(T)=\frac{\left[\begin{array}{c} K_1^a\int_0^T C_p^T(t)\,dt \\ -\left(\dfrac{K_1^a\,\frac{\Delta t}{2}\,\dfrac{k_2^m}{1+\frac{\Delta t}{2}k_2^m}}{1+\frac{\Delta t}{2}K_1^m\left(1-\dfrac{\frac{\Delta t}{2}k_2^m}{1+\frac{\Delta t}{2}k_2^m}\right)}\right)\left[\int_0^{T-\Delta t} C_t^m(t)\,dt+\frac{\Delta t}{2}C_t^m(T-\Delta t)\right] \\ -\left(\dfrac{K_1^a}{1+\frac{\Delta t}{2}K_1^m\left(1-\dfrac{\frac{\Delta t}{2}k_2^m}{1+\frac{\Delta t}{2}k_2^m}\right)}\right)\left[\int_0^{T-\Delta t} C_p^m(t)\,dt+\frac{\Delta t}{2}C_p^m(T-\Delta t)\right] \\ -\left(k_2^a+k_3+\dfrac{K_1^a k_3\left(\frac{\Delta t}{2}\right)^2\dfrac{k_2^m}{1+\frac{\Delta t}{2}k_2^m}}{1+\frac{\Delta t}{2}K_1^m\left(1-\dfrac{\frac{\Delta t}{2}k_2^m}{1+\frac{\Delta t}{2}k_2^m}\right)}\right)\left[\int_0^{T-\Delta t} C_t^a(t)\,dt+\frac{\Delta t}{2}C_t^a(T-\Delta t)\right] \end{array}\right]}{1+\frac{\Delta t}{2}\left(k_2^a+k_3+\dfrac{K_1^a k_3\left(\frac{\Delta t}{2}\right)^2\dfrac{k_2^m}{1+\frac{\Delta t}{2}k_2^m}}{1+\frac{\Delta t}{2}K_1^m\left(1-\dfrac{\frac{\Delta t}{2}k_2^m}{1+\frac{\Delta t}{2}k_2^m}\right)}\right)} \qquad (9)$$

References

1. Carson RE, Breier A, de Bartolomeis A, Saunders RC, Su TP, Schmall B, Der MG, Pickar D, Eckelman WC. Quantification of amphetamine-induced changes in [^{11}C]-raclopride binding with continuous infusion. *J Cereb Blood Flow Metab* 1997; 17: 437-447.
2. 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.