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Huang'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 Huang et al. (1991). The ODEs are solved using the second order Adams-Moulton method with trapezoidal rule [Kuwabara et al. 1993].

Compartmental model

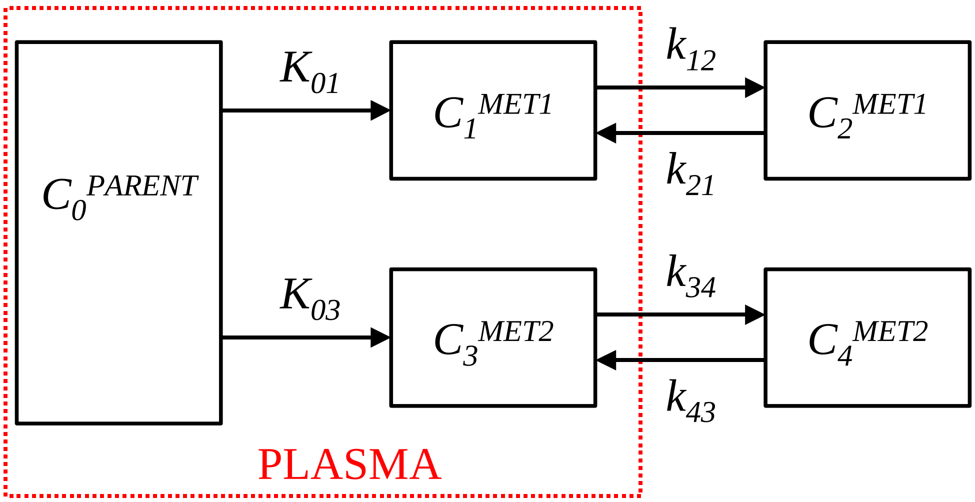

Fig. A1-1. Generalized compartment model for PET tracers with two labelled metabolites, originally developed and validated for $[^{18}F]$FDOPA PET studies by Huang et al. (1991). The model equals the one developed for $[^{15}O]O_2$ by the same authors, if the second metabolite is excluded by setting $K_{03}=0$.

Differential equations

$$dC_1^{MET1}(t)/dt = K_{01}C_0^{PARENT}(t) + k_{21}C_2^{MET1}(t) - k_{12}C_1^{MET1}(t) \quad (1)$$
$$dC_2^{MET1}(t)/dt = k_{12}C_1^{MET1}(t) - k_{21}C_2^{MET1}(t) \quad (2)$$
$$dC_3^{MET2}(t)/dt = K_{03}C_0^{PARENT}(t) + k_{43}C_4^{MET2}(t) - k_{34}C_3^{MET2}(t) \quad (3)$$
$$dC_4^{MET2}(t)/dt = k_{34}C_3^{MET2}(t) - k_{43}C_4^{MET2}(t) \quad (4)$$

Note that the models for both metabolites are similar, and therefore also the equations for them are equivalent.

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

$$C_0^{PARENT}(t) = C_{PLASMA}^{TOTAL}(t) - C_1^{MET1}(t) - C_3^{MET2}(t) \quad (5)$$

Substitution of Eq (5) (the unknown concentration of parent tracer) into Eqs. (1) and (3) gives

$$dC_1^{MET1}(t)/dt = K_{01}C_{PLASMA}^{TOTAL}(t) - (K_{01}+k_{12})C_1^{MET1}(t) - K_{01}C_3^{MET2}(t) + k_{21}C_2^{MET1}(t) \quad (6)$$
$$dC_3^{MET2}(t)/dt = K_{03}C_{PLASMA}^{TOTAL}(t) - (K_{03}+k_{34})C_3^{MET2}(t) - K_{03}C_1^{MET1}(t) + k_{43}C_4^{MET2}(t) \quad (7)$$

Integration of Eqs. (2) and (4), and solving using the second order Adams-Moulton method with trapezoidal rule gives equations for the concentrations of metabolites in tissue compartments and their integrals. (Concentrations at time point 0 are assumed to be 0).

$$C_2^{MET1}(T) = \frac{k_{12}\int_0^T C_1^{MET1}(t)dt - k_{21}\left[\int_0^{T-\Delta t} C_2^{MET1}(t)dt + \tfrac{\Delta t}{2}C_2^{MET1}(T-\Delta t)\right]}{1+\tfrac{\Delta t}{2}k_{21}} \quad (8)$$
$$C_4^{MET2}(T) = \frac{k_{34}\int_0^T C_3^{MET2}(t)dt - k_{43}\left[\int_0^{T-\Delta t} C_4^{MET2}(t)dt + \tfrac{\Delta t}{2}C_4^{MET2}(T-\Delta t)\right]}{1+\tfrac{\Delta t}{2}k_{43}} \quad (9)$$

$$\int_0^T C_2^{MET1}(t)dt = \frac{k_{12}\tfrac{\Delta t}{2}}{1+\tfrac{\Delta t}{2}k_{21}}\int_0^T C_1^{MET1}(t)dt + \frac{\left[\int_0^{T-\Delta t} C_2^{MET1}(t)dt + \tfrac{\Delta t}{2}C_2^{MET1}(T-\Delta t)\right]}{1+\tfrac{\Delta t}{2}k_{21}} \quad (10)$$
$$\int_0^T C_4^{MET2}(t)dt = \frac{k_{34}\tfrac{\Delta t}{2}}{1+\tfrac{\Delta t}{2}k_{43}}\int_0^T C_3^{MET2}(t)dt + \frac{\left[\int_0^{T-\Delta t} C_4^{MET2}(t)dt + \tfrac{\Delta t}{2}C_4^{MET2}(T-\Delta t)\right]}{1+\tfrac{\Delta t}{2}k_{43}} \quad (11)$$

Substitution of Eq. (10) into integrated form of Eq. (6), and Eq. (11) into integrated form of Eq. (7), will give formulas (12) and (13):

$$\begin{aligned} C_1^{MET1}(T) = \quad & K_{01}\int_0^T C_{PLASMA}^{TOTAL}(t)dt - K_{01}\int_0^T C_3^{MET2}(t)dt - A\int_0^T C_1^{MET1}(t)dt \\ & + \frac{k_{21}}{1+\tfrac{\Delta t}{2}k_{21}}\left[\int_0^{T-\Delta t} C_2^{MET1}(t)dt + \tfrac{\Delta t}{2}C_2^{MET1}(T-\Delta t)\right] \quad (12) \end{aligned}$$
$$\begin{aligned} C_3^{MET2}(T) = \quad & K_{03}\int_0^T C_{PLASMA}^{TOTAL}(t)dt - K_{03}\int_0^T C_1^{MET1}(t)dt - B\int_0^T C_3^{MET2}(t)dt \\ & + \frac{k_{43}}{1+\tfrac{\Delta t}{2}k_{43}}\left[\int_0^{T-\Delta t} C_4^{MET2}(t)dt + \tfrac{\Delta t}{2}C_4^{MET2}(T-\Delta t)\right] \quad (13) \end{aligned}$$

where A and B are:

$$A = K_{01} + k_{12} - \frac{k_{12}k_{21}\tfrac{\Delta t}{2}}{1+\tfrac{\Delta t}{2}k_{21}} \qquad B = K_{03} + k_{34} - \frac{k_{34}k_{43}\tfrac{\Delta t}{2}}{1+\tfrac{\Delta t}{2}k_{43}}$$

The integrals of plasma metabolites are solved using the second order Adams-Moulton method with trapezoidal rule, again assuming that concentrations at time point 0 are zero:

$$\int_0^T C_1^{MET1}(t)dt = \frac{K_{01}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}A}\int_0^T C_{PLASMA}^{TOTAL}(t)dt - \frac{K_{01}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}A}\int_0^T C_3^{MET2}(t)dt + \frac{\frac{k_{21}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}k_{21}}\left[\int_0^{T-\Delta t} C_2^{MET1}(t)dt + \frac{\Delta t}{2}C_2^{MET1}(T-\Delta t)\right] + \left[\int_0^{T-\Delta t} C_1^{MET1}(t)dt + \frac{\Delta t}{2}C_1^{MET1}(T-\Delta t)\right]}{1+\frac{\Delta t}{2}A} \tag{14}$$

$$\int_0^T C_3^{MET2}(t)dt = \frac{K_{03}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}B}\int_0^T C_{PLASMA}^{TOTAL}(t)dt - \frac{K_{03}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}B}\int_0^T C_1^{MET1}(t)dt + \frac{\frac{k_{43}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}k_{43}}\left[\int_0^{T-\Delta t} C_4^{MET2}(t)dt + \frac{\Delta t}{2}C_4^{MET2}(T-\Delta t)\right] + \left[\int_0^{T-\Delta t} C_3^{MET2}(t)dt + \frac{\Delta t}{2}C_3^{MET2}(T-\Delta t)\right]}{1+\frac{\Delta t}{2}B} \tag{15}$$

Substitution of Eq. (15) into Eq. (12) and solving using the second order Adams-Moulton method with trapezoidal rule gives equations gives Eq. (16), which can be used to calculate the concentration of first plasma metabolite one sample at a time. Eq. (17) for the second metabolite is solved similarly.

$$C_1^{MET1}(T) = \frac{\left\{\begin{aligned} &K_{01}\left(1-\frac{K_{03}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}B}\right)\int_0^T C_{PLASMA}^{TOTAL}(t)dt \\ &-\left(A-\frac{K_{01}K_{03}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}B}\right)\left[\int_0^{T-\Delta t} C_1^{MET1}(t)dt + \frac{\Delta t}{2}C_1^{MET1}(T-\Delta t)\right] \\ &+\frac{k_{21}}{1+\frac{\Delta t}{2}k_{21}}\left[\int_0^{T-\Delta t} C_2^{MET1}(t)dt + \frac{\Delta t}{2}C_2^{MET1}(T-\Delta t)\right] \\ &-\frac{K_{01}}{1+\frac{\Delta t}{2}B}\left[\int_0^{T-\Delta t} C_3^{MET2}(t)dt + \frac{\Delta t}{2}C_3^{MET2}(T-\Delta t)\right] \\ &-\frac{K_{01}k_{43}\frac{\Delta t}{2}}{\left(1+\frac{\Delta t}{2}B\right)\left(1+\frac{\Delta t}{2}k_{43}\right)}\left[\int_0^{T-\Delta t} C_4^{MET2}(t)dt + \frac{\Delta t}{2}C_4^{MET2}(T-\Delta t)\right] \end{aligned}\right\}}{1+\frac{\Delta t}{2}\left(A-\frac{K_{01}K_{03}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}B}\right)} \tag{16}$$

$$C_3^{MET2}(T) = \frac{\left\{\begin{aligned} &K_{03}\left(1-\frac{K_{01}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}A}\right)\int_0^T C_{PLASMA}^{TOTAL}(t)dt \\ &-\left(B-\frac{K_{01}K_{03}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}A}\right)\left[\int_0^{T-\Delta t} C_3^{MET2}(t)dt + \frac{\Delta t}{2}C_3^{MET2}(T-\Delta t)\right] \\ &+\frac{k_{43}}{1+\frac{\Delta t}{2}k_{43}}\left[\int_0^{T-\Delta t} C_4^{MET2}(t)dt + \frac{\Delta t}{2}C_4^{MET2}(T-\Delta t)\right] \\ &-\frac{K_{03}}{1+\frac{\Delta t}{2}A}\left[\int_0^{T-\Delta t} C_1^{MET1}(t)dt + \frac{\Delta t}{2}C_1^{MET1}(T-\Delta t)\right] \\ &-\frac{K_{03}k_{21}\frac{\Delta t}{2}}{\left(1+\frac{\Delta t}{2}A\right)\left(1+\frac{\Delta t}{2}k_{21}\right)}\left[\int_0^{T-\Delta t} C_2^{MET1}(t)dt + \frac{\Delta t}{2}C_2^{MET1}(T-\Delta t)\right] \end{aligned}\right\}}{1+\frac{\Delta t}{2}\left(B-\frac{K_{01}K_{03}\frac{\Delta t}{2}}{1+\frac{\Delta t}{2}A}\right)} \tag{17}$$

References

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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.