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Graham's plasma time-activity curve model for parent tracer and a metabolite

This document described the Graham's input function model [Graham, 1997], extended with compartments for a single labelled plasma metabolite, and the mathematical equations required for simulating them. The ODEs are solved using the second-order Adams-Moulton method with trapezoidal rule [Kuwabara et al., 1993].

Model description

Compartmental model

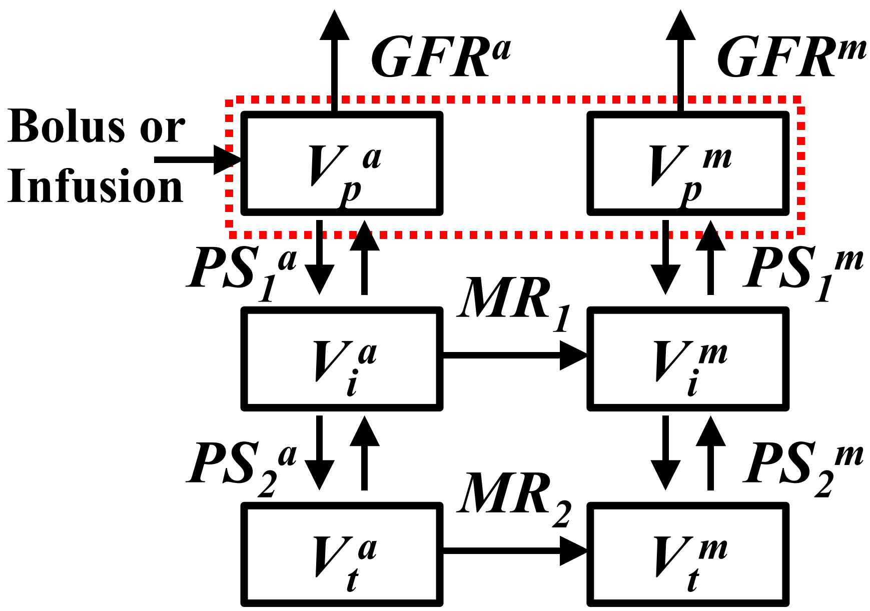

Fig. B1-1. Grahams's compartmental model extended with compartments for a metabolite.

Table B1-1. Descriptions of the model parameters.

C_p^a	Concentration of parent tracer in plasma	$kBq\ mL^{-1}$
C_i^a	Concentration of parent tracer in interstitial fluid	$kBq\ mL^{-1}$
C_t^a	Concentration of parent tracer in tissue fluid	$kBq\ mL^{-1}$
V_p^a	Volume of plasma for parent tracer	$mL\ mL^{-1}$
V_i^a	Volume of interstitial fluid for parent tracer	$mL\ mL^{-1}$
V_t^a	Volume of tissue fluid for parent tracer	$mL\ mL^{-1}$
PS_1^a	Permeability-surface area product (*PS*) for exchange from V_p^a to V_i^a	$mL\ min^{-1}\ mL^{-1}$
PS_2^a	*PS* for exchange from V_i^a to V_t^a	$mL\ min^{-1}\ mL^{-1}$
GFR^a	Glomerular filtration rate for parent tracer	$mL\ min^{-1}\ mL^{-1}$
MR_1	Rate of metabolism in interstitial volume	$mL\ min^{-1}\ mL^{-1}$
MR_2	Rate of metabolism in tissue fluid volume	$mL\ min^{-1}\ mL^{-1}$
C_p^m	Concentration of metabolized tracer in plasma	$kBq\ mL^{-1}$
C_i^m	Concentration of metabolized tracer in interstitial fluid	$kBq\ mL^{-1}$
C_t^m	Concentration of metabolized tracer in tissue fluid	$kBq\ mL^{-1}$
V_p^m	Volume of plasma for metabolized tracer	$mL\ mL^{-1}$
V_i^m	Volume of interstitial fluid for metabolized tracer	$mL\ mL^{-1}$
V_t^m	Volume of tissue fluid for metabolized tracer	$mL\ mL^{-1}$
PS_1^m	*PS* for exchange from V_p^m to V_i^m	$mL\ min^{-1}\ mL^{-1}$
PS_2^m	*PS* for exchange from V_i^m to V_t^m	$mL\ min^{-1}\ mL^{-1}$
GFR^m	Glomerular filtration rate for metabolized tracer	$mL\ min^{-1}\ mL^{-1}$
H	Amount of activity infused per min	$kBq\ min^{-1}\ mL^{-1}$
H'	H at the end of the infusion period; $H'=H*(1-exp(-k*Dur))$	$kBq\ min^{-1}\ mL^{-1}$
k	Time constant	min^{-1}
Delay	Time before bolus reaches the measurement point	*min*
Dur	Duration of infusion; in bolus injection $Dur=0$	*min*

Simulation of bolus and infusion

The equations for bolus input (1) and infusion (2) are:

$$Input(t) = \begin{Bmatrix} 0 & ,t < Delay \\ H \times e^{-k(t-Delay)} & ,t \geq Delay \end{Bmatrix} \tag{1}$$

$$Input(t) = \begin{Bmatrix} 0 & ,t < Delay \\ H \times \left(1 - e^{-k(t-Delay)}\right) & ,Delay \geq t > Delay + Dur \\ H' \times e^{-k(t-Delay-Dur)} & ,t \geq Delay + Dur \end{Bmatrix} \tag{2}$$

Integral of input

The equations for bolus injection integral from time *0* to *T* is

$$\int_0^T Input(t)dt = \begin{Bmatrix} 0 & , T < Delay \\ \dfrac{H}{k}\left(1 - e^{-k \times (T-Delay)}\right) & , T \geq Delay \end{Bmatrix} \tag{3}$$

and for infusion integral:

$$\int_0^T Input(t)dt = \begin{Bmatrix} 0 & ,T < Delay \\ H(T - Delay) - \dfrac{H}{k}\left(1 - e^{-k \times (T-Delay)}\right) & , Delay \leq T < Delay + Dur \\ H \times Dur - \dfrac{H}{k}\left(1 - e^{-k \times Dur}\right) e^{-k \times (T-Delay-Dur)} & ,T \geq Delay + Dur \end{Bmatrix} \tag{4}$$

Differential equations for the concentrations in model compartments

$$V_p^a \frac{dC_p^a(t)}{dt} = \quad Input(t) - \left(PS_1^a + GFR^a\right) \times C_p^a(t) + PS_1^a \times C_i^a(t) \tag{5}$$

$$V_i^a \frac{dC_i^a(t)}{dt} = \quad PS_1^a \times C_p^a(t) + PS_2^a \times C_t^a(t) - \left(PS_1^a + PS_2^a + MR_1\right) \times C_i^a(t) \tag{6}$$

$$V_t^a \frac{dC_t^a(t)}{dt} = \quad PS_2^a \times C_i^a(t) - \left(PS_2^a + MR_2\right) \times C_t^a(t) \tag{7}$$

$$V_p^m \frac{dC_p^m(t)}{dt} = \quad PS_1^m \times C_i^m(t) - \left(PS_1^m + GFR^m\right) \times C_p^m(t) \tag{8}$$

$$V_i^m \frac{dC_i^m(t)}{dt} = \quad MR_1 \times C_i^a(t) + PS_1^m \times C_p^m(t) + PS_2^m \times C_t^m(t) - \left(PS_1^m + PS_2^m\right) \times C_i^m(t) \tag{9}$$

$$V_t^m \frac{dC_t^m(t)}{dt} = \quad MR_2 \times C_t^a(t) + PS_2^m \times C_i^m(t) - PS_2^m \times C_t^m(t) \tag{10}$$

Solving differential equations

Integration of Eq. (7) and solving using the second order Adams-Moulton method with trapezoidal rule (concentrations at time *0* are assumed to be *0*) gives the equations for the concentration of parent tracer in tissue compartment and its integral:

$$C_t^a(T) = \frac{PS_2^a \int_0^T C_i^a(t)dt - \left(PS_2^a + MR_2\right)\left[\int_0^{T-\Delta t} C_t^a(t)dt + \frac{\Delta t}{2} C_t^a(T-\Delta t)\right]}{V_t^a + \frac{\Delta t}{2}\left(PS_2^a + MR_2\right)} \qquad (11)$$

$$\int_0^T C_t^a(t)dt = \frac{PS_2^a \frac{\Delta t}{2} \int_0^T C_i^a(t)dt + V_t^a \left[\int_0^{T-\Delta t} C_t^a(t)dt + \frac{\Delta t}{2} C_t^a(T-\Delta t)\right]}{V_t^a + \frac{\Delta t}{2}\left(PS_2^a + MR_2\right)} \qquad (12)$$

Integration of Eq. (6), substitution of Eq. (12) and solving gives the equations for the concentration of parent tracer in intersitial volume and its integral:

$$C_i^a(T) = \frac{\left\{\begin{array}{c} PS_1^a \int_0^T C_p^a(t)dt + A V_t^a \left[\int_0^{T-\Delta t} C_t^a(t)dt + \frac{\Delta t}{2} C_t^a(T-\Delta t)\right] \\ - \left(PS_1^a + MR_1 + PS_2^a\left(1 - \frac{\Delta t}{2} A\right)\right)\left[\int_0^{T-\Delta t} C_i^a(t)dt + \frac{\Delta t}{2} C_i^a(T-\Delta t)\right] \end{array}\right\}}{V_i^a + \frac{\Delta t}{2}\left(PS_1^a + MR_1 + PS_2^a\left(1 - \frac{\Delta t}{2} A\right)\right)} \qquad (13)$$

$$\int_0^T C_i^a(t)dt = \frac{\left\{\begin{array}{c} PS_1^a \frac{\Delta t}{2} \int_0^T C_p^a(t)dt + A V_t^a \frac{\Delta t}{2}\left[\int_0^{T-\Delta t} C_t^a(t)dt + \frac{\Delta t}{2} C_t^a(T-\Delta t)\right] \\ + V_i^a \left[\int_0^{T-\Delta t} C_i^a(t)dt + \frac{\Delta t}{2} C_i^a(T-\Delta t)\right] \end{array}\right\}}{V_i^a + \frac{\Delta t}{2}\left(PS_1^a + MR_1 + PS_2^a\left(1 - \frac{\Delta t}{2} A\right)\right)} \qquad (14)$$

, where $A = PS_2^a/(V_t^a + (\Delta t/2) * (PS_2^a + MR_2))$. Integration of Eq. (5), substitution of Eq. (14) and solving gives the equation for the concentration of parent tracer in plasma volume:

$$C_p^a(T) = \frac{\left\{\begin{array}{c} \int_0^T Input(t)dt \\ - \left(GFR^a + PS_1^a\left(1 - \frac{\Delta t}{2} B\right)\right)\left[\int_0^{T-\Delta t} C_p^a(t)dt + \frac{\Delta t}{2} C_p^a(T-\Delta t)\right] \\ + A\, B\, V_t^a \frac{\Delta t}{2}\left[\int_0^{T-\Delta t} C_t^a(t)dt + \frac{\Delta t}{2} C_t^a(T-\Delta t)\right] \\ + B\, V_i^a \left[\int_0^{T-\Delta t} C_i^a(t)dt + \frac{\Delta t}{2} C_i^a(T-\Delta t)\right] \end{array}\right\}}{V_p^a + \frac{\Delta t}{2}\left(GFR^a + PS_1^a\left(1 - \frac{\Delta t}{2} B\right)\right)} \qquad (15)$$

, where $B = PS_1^a/(V_i^a + (\Delta t/2) * (PS_1^a + MR_1 + PS_2^a * (1 - (\Delta t/2) * A)))$.

Integration of Eq. (10) and solving gives equations for the concentration of labeled metabolite in tissue volume and its integral:

$$C_t^m(T) = \frac{MR_2 \int_0^T C_t^a(t)dt + PS_2^m \int_0^T C_i^m(t)dt - PS_2^m \left[\int_0^{T-\Delta t} C_t^m(t)dt + \frac{\Delta t}{2} C_t^m(T-\Delta t) \right]}{V_t^m + \frac{\Delta t}{2} PS_2^m} \tag{16}$$

$$\int_0^T C_t^m(t)dt = \frac{MR_2 \frac{\Delta t}{2} \int_0^T C_t^a(t)dt + PS_2^m \frac{\Delta t}{2} \int_0^T C_i^m(t)dt + V_t^m \left[\int_0^{T-\Delta t} C_t^m(t)dt + \frac{\Delta t}{2} C_t^m(T-\Delta t) \right]}{V_t^m + \frac{\Delta t}{2} PS_2^m} \tag{17}$$

Integration of Eq. (9), substitution of Eq. (17) and solving gives the equations for the concentration of metabolite in intersitial volume and its integral:

$$C_i^m(T) = \frac{\left\{ \begin{array}{c} MR_1 \int_0^T C_i^a(t)dt + PS_1^m \int_0^T C_p^m(t)dt + D\, MR_2 \frac{\Delta t}{2} \int_0^T C_t^a(t)dt \\ + D\, V_t^m \left[\int_0^{T-\Delta t} C_t^m(t)dt + \frac{\Delta t}{2} C_t^m(T-\Delta t) \right] \\ -\left(PS_1^m + PS_2^m\left(1 - \frac{\Delta t}{2} D\right)\right) \left[\int_0^{T-\Delta t} C_i^m(t)dt + \frac{\Delta t}{2} C_i^m(T-\Delta t) \right] \end{array} \right\}}{V_i^m + \frac{\Delta t}{2}\left(PS_1^m + PS_2^m\left(1 - \frac{\Delta t}{2} D\right)\right)} \tag{18}$$

$$\int_0^T C_i^m(t)dt = \frac{\left\{ \begin{array}{c} MR_1 \frac{\Delta t}{2} \int_0^T C_i^a(t)dt + PS_1^m \frac{\Delta t}{2} \int_0^T C_p^m(t)dt + D\, MR_2 \left(\frac{\Delta t}{2}\right)^2 \int_0^T C_t^a(t)dt \\ + D\, V_t^m \frac{\Delta t}{2} \left[\int_0^{T-\Delta t} C_t^m(t)dt + \frac{\Delta t}{2} C_t^m(T-\Delta t) \right] \\ + V_i^m \left[\int_0^{T-\Delta t} C_i^m(t)dt + \frac{\Delta t}{2} C_i^m(T-\Delta t) \right] \end{array} \right\}}{V_i^m + \frac{\Delta t}{2}\left(PS_1^m + PS_2^m\left(1 - \frac{\Delta t}{2} D\right)\right)} \tag{19}$$

, where $D=PS_2^m/(V_t^m+(\Delta t/2)*PS_2^m)$. Integration of Eq. (8), substitution of Eq. (19) and solving gives the equation for the concentration of metabolized tracer in plasma volume:

$$C_p^m(T) = \frac{\left\{ \begin{array}{c} E\, MR_1 \frac{\Delta t}{2} \int_0^T C_i^a(t)dt + D\, E\, MR_2 \left(\frac{\Delta t}{2}\right)^2 \int_0^T C_t^a(t)dt \\ -\left(GFR^m + PS_1^m\left(1 - \frac{\Delta t}{2} E\right)\right) \left[\int_0^{T-\Delta t} C_p^m(t)dt + \frac{\Delta t}{2} C_p^m(T-\Delta t) \right] \\ + D\, E\, V_t^m \frac{\Delta t}{2} \left[\int_0^{T-\Delta t} C_t^m(t)dt + \frac{\Delta t}{2} C_t^m(T-\Delta t) \right] \\ + E\, V_i^m \left[\int_0^{T-\Delta t} C_i^m(t)dt + \frac{\Delta t}{2} C_i^m(T-\Delta t) \right] \end{array} \right\}}{V_p^m + \frac{\Delta t}{2}\left(GFR^m + PS_1^m\left(1 - \frac{\Delta t}{2} E\right)\right)} \tag{20}$$

, where $E=PS_1^m/(V_i^m+(\Delta t/2)*(PS_1^m+PS_2^m*(1-(\Delta t/2)*D)))$.

The original Graham's model can be derived from the extended model by setting the parameters of the extension compartment (PS_3, V_c) to zero.

References

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