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Graham's plasma time-activity curve model

This document described the original Graham's input function model [Graham, 1997], its extension, 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

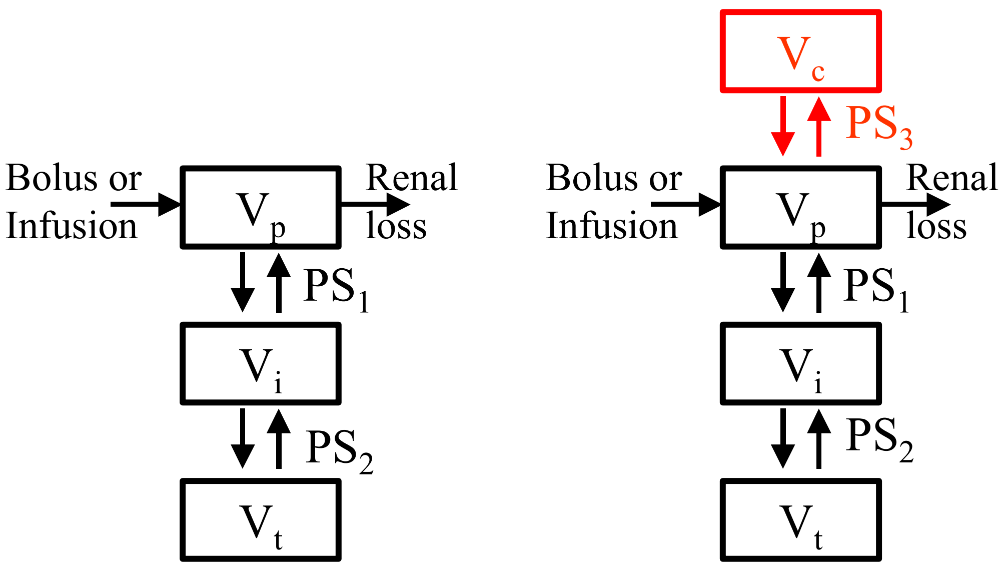

Fig. A1-1. Original Grahams's compartmental model (left), and the modification of it, which includes a compartment for blood cells (right).

The structures of the compartmental models are described in Fig. A1-1, the variables in Table A1-1, and the differential equations (1-4) are given below:

$$V_p \, dC_p(t)/dt = Input(t) - (PS_1 + GFR + PS_3) \times C_p(t) + PS_1 \times C_i(t) + PS_3 \times C_c(t) \quad (1)$$

$$V_i \, dC_i(t)/dt = PS_1 \times C_p(t) + PS_2 \times C_t(t) - (PS_1 + PS_2) \times C_i(t) \quad (2)$$

$$V_t \, dC_t(t)/dt = PS_2 \times C_i(t) - PS_2 \times C_t(t) \quad (3)$$

$$V_c \, dC_c(t)/dt = PS_3 \times C_p(t) - PS_3 \times C_c(t) \quad (4)$$

Simulation of bolus and infusion

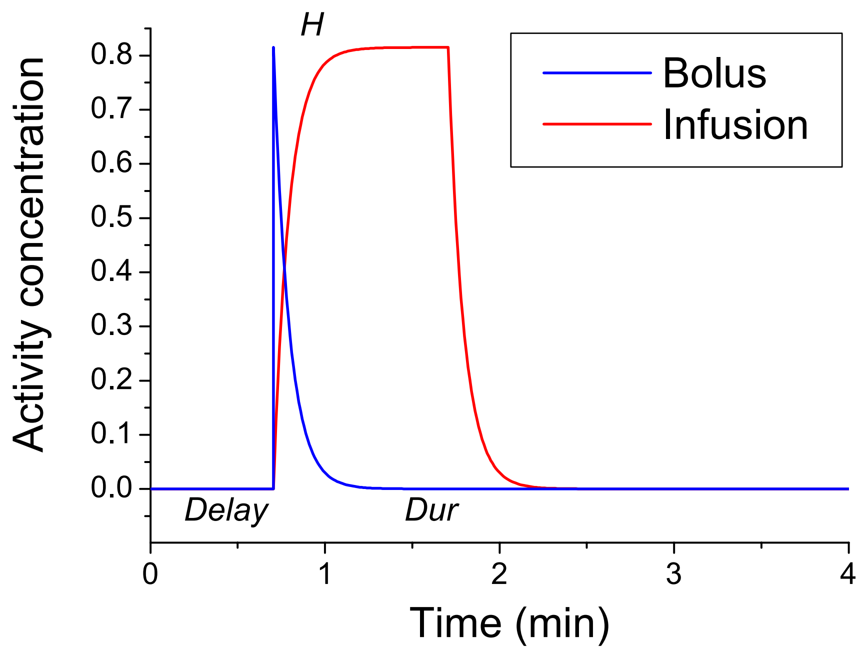

Fig. A1-2. Bolus injection (red) and infusion (red) simulated with the same parameters as in Grahams's study [Graham 1997]: H=0.815, k=11.2, Dur=0.0 (bolus) or Dur=1.0 (Infusion), Delay=0.7052.

The equations for bolus input (5) and infusion (6) are:

$$Input(t) = \begin{Bmatrix} 0 & ,t < Delay \\ H \times e^{-k(t-Delay)} & ,t \geq Delay \end{Bmatrix} \quad (5)$$

$$Input(t) = \begin{Bmatrix} 0 & ,t < Delay \\ H \times \left(1 - e^{-k(t-Delay)}\right) & ,Delay \geq t > Delay + Dur \\ H' \times e^{-k(t-Delay-Dur)} & ,t \geq Delay + Dur \end{Bmatrix} \quad (6)$$

Table A1-1. Descriptions of the model parameters.

C_p	Concentration of tracer in plasma	$kBq\ mL^{-1}$
C_c	Concentration of tracer in blood cell fluid	$kBq\ mL^{-1}$
C_i	Concentration of tracer in interstitial fluid	$kBq\ mL^{-1}$
C_t	Concentration of tracer in tissue fluid	$kBq\ mL^{-1}$
V_p	Volume of plasma	$mL\ mL^{-1}$
V_c	Volume of blood cell fluid	$mL\ mL^{-1}$
V_i	Volume of interstitial fluid	$mL\ mL^{-1}$
V_t	Volume of tissue fluid	$mL\ mL^{-1}$
PS_1	Permeability-surface area product (*PS*) for exchange from V_p to V_i	$mL\ min^{-1}\ mL^{-1}$
PS_2	*PS* for exchange from V_i to V_t	$mL\ min^{-1}\ mL^{-1}$
PS_3	*PS* for exchange from V_p to V_c	$mL\ min^{-1}\ mL^{-1}$
GFR	Glomerular filtration rate	$mL\ min^{-1}\ mL^{-1}$
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*

Solving differential equations

Original Graham's model

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.

Extended model

The integrated forms of the equations (1-3) are as follows, when the parts of the extended model are excluded from those:

$$V_p C_p(T) = \int_0^T Input(t)dt - \left(PS_1 + GFR + PS_3\right)\int_0^T C_p(t)dt + PS_1 \int_0^T C_i(t)dt + PS_3 \int_0^T C_c(t)dt \quad (7)$$

$$V_i C_i(T) = PS_1 \int_0^T C_p(t)dt - \left(PS_1 + PS_2\right)\int_0^T C_i(t)dt + PS_2 \int_0^T C_t(t)dt \quad (8)$$

$$V_t C_t(T) = PS_2 \int_0^T C_i(t)dt - PS_2 \int_0^T C_t(t)dt \quad (9)$$

$$V_c C_c(T) = PS_3 \int_0^T C_p(t)dt - PS_3 \int_0^T C_c(t)dt \quad (10)$$

By applying the second-order Adams-Moulton method with trapezoidal rule, the integral of radioactivity concentration in compartment *n* can be presented as in Eq. (11), and the compartmental concentration can be solved as in Eq. (12); Δt is the difference between sample collection times:

$$\int_0^T C_N(t)dt = \frac{\Delta t}{2} C_N(T) + \left(\int_0^{T-\Delta t} C_N(t)dt + \frac{\Delta t}{2} C_N(T - \Delta t) \right) \quad (11)$$

$$C_N(T) = \frac{1}{\Delta t/2} \int_0^T C_N(t)dt - \frac{1}{\Delta t/2} \left(\int_0^{T-\Delta t} C_N(t)dt + \frac{\Delta t}{2} C_N(T - \Delta t) \right) \quad (12)$$

Substitution of Eq. (11) into Eq. (10) gives the equation for $C_c(T)$, and substitution of Eq. (12) into Eq. (10) gives the equation for its integral (14), which is needed to solve further equations:

$$C_c(T) = \frac{PS_3 \int_0^T C_p(t)dt - PS_3 \left[\int_0^{T-\Delta t} C_c(t)dt + \frac{\Delta t}{2} C_c(T - \Delta t) \right]}{V_c + PS_3 \frac{\Delta t}{2}} \quad (13)$$

$$\int_0^T C_c(t)dt = \frac{PS_3 \frac{\Delta t}{2}}{V_c + PS_3 \frac{\Delta t}{2}} \int_0^T C_p(t)dt + \frac{V_c}{V_c + PS_3 \frac{\Delta t}{2}} \left[\int_0^{T-\Delta t} C_c(t)dt + \frac{\Delta t}{2} C_c(T - \Delta t) \right] \quad (14)$$

In the same manner substitution of equations (11) and (12) into equation (9) gives the expressions for $C_t(T)$ and its integral:

$$C_t(T) = \frac{PS_2 \int_0^T C_i(t)dt - PS_2 \left[\int_0^{T-\Delta t} C_t(t)dt + \frac{\Delta t}{2} C_t(T-\Delta t) \right]}{V_t + PS_2 \frac{\Delta t}{2}} \quad (15)$$

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

Substitution of Eq. (16) into Eq. (8), and then substitution of Eq. (11), gives the equation for $C_i(T)$:

$$C_i(T) = \frac{\left\{ \begin{array}{c} PS_1 \int_0^T C_p(t)dt \\ -\left(PS_1 + \frac{PS_2 V_t}{V_t + PS_2 \frac{\Delta t}{2}} \right) \left[\int_0^{T-\Delta t} C_i(t)dt + \frac{\Delta t}{2} C_i(T-\Delta t) \right] \\ +\left(\frac{PS_2 V_t}{V_t + PS_2 \frac{\Delta t}{2}} \right) \left[\int_0^{T-\Delta t} C_t(t)dt + \frac{\Delta t}{2} C_t(T-\Delta t) \right] \end{array} \right\}}{V_i + \frac{\Delta t}{2} \left(PS_1 + \frac{PS_2 V_t}{V_t + PS_2 \frac{\Delta t}{2}} \right)} \quad (17)$$

Substitution of Eq. (12) and (16) into Eq. (8) gives the equation for *$C_i(T)$'s* integral:

$$\int_0^T C_i(t)dt = \frac{\left\{ \begin{array}{c} PS_1 \frac{\Delta t}{2} \int_0^T C_p(t)dt \\ +V_i \left[\int_0^{T-\Delta t} C_i(t)dt + \frac{\Delta t}{2} C_i(T-\Delta t) \right] \\ +\left(\frac{PS_2 V_t \frac{\Delta t}{2}}{V_t + PS_2 \frac{\Delta t}{2}} \right) \left[\int_0^{T-\Delta t} C_t(t)dt + \frac{\Delta t}{2} C_t(T-\Delta t) \right] \end{array} \right\}}{V_i + \frac{\Delta t}{2} \left(PS_1 + \frac{PS_2 V_t}{V_t + PS_2 \frac{\Delta t}{2}} \right)} \quad (18)$$

In the next step $C_p(T)$ is solved by substitution of Eq. (14) and (18) into Eq. (7), and then substitution of Eq. (11):

$$C_p(T)=\frac{\left\{\begin{array}{l}\int_0^T Input(t)dt \\ -\left(GFR+\frac{PS_1V_iV_t+PS_1PS_2\frac{\Delta t}{2}(V_i+V_t)}{V_iV_t+\frac{\Delta t}{2}(V_iPS_2+V_tPS_1+\frac{\Delta t}{2}PS_1PS_2+V_tPS_2)}+\frac{PS_3V_c}{V_c+PS_3\frac{\Delta t}{2}}\right) \\ \qquad\times\left[\int_0^{T-\Delta t}C_p(t)dt+\frac{\Delta t}{2}C_p(T-\Delta t)\right] \\ +\left(\frac{PS_1}{V_i+\frac{\Delta t}{2}(PS_1+\frac{PS_2V_t}{V_t+PS_2\frac{\Delta t}{2}})}\right) \\ \quad\times\left[V_i\left[\int_0^{T-\Delta t}C_i(t)dt+\frac{\Delta t}{2}C_i(T-\Delta t)\right]+\frac{PS_2V_t\frac{\Delta t}{2}}{V_t+PS_2\frac{\Delta t}{2}}\left(\int_0^{T-\Delta t}C_t(t)dt+\frac{\Delta t}{2}C_t(T-\Delta t)\right)\right] \\ +\frac{PS_3V_c}{V_c+PS_3\frac{\Delta t}{2}}\left[\int_0^{T-\Delta t}C_c(t)dt+\frac{\Delta t}{2}C_c(T-\Delta t)\right]\end{array}\right\}}{V_p+\frac{\Delta t}{2}\left(GFR+\frac{PS_1V_iV_t+PS_1PS_2\frac{\Delta t}{2}(V_i+V_t)}{V_iV_t+\frac{\Delta t}{2}\left(V_iPS_2+V_tPS_1+\frac{\Delta t}{2}PS_1PS_2+V_tPS_2\right)}+\frac{PS_3V_c}{V_c+PS_3\frac{\Delta t}{2}}\right)} \tag{19}$$

Integral of input

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

$$\int_0^T Input(t)dt=\left\{\begin{array}{ll}0 & ,T<Delay \\ \frac{H}{k}\left(1-e^{-k\times(T-Delay)}\right) & ,T\geq Delay\end{array}\right\} \tag{20}$$

and for infusion integral:

$$\int_0^T Input(t)dt=\left\{\begin{array}{ll}0 & ,T<Delay \\ H(T-Delay)-\frac{H}{k}\left(1-e^{-k\times(T-Delay)}\right) & ,Delay\leq T<Delay+Dur \\ H\times Dur-\frac{H}{k}\left(1-e^{-k\times Dur}\right)e^{-k\times(T-Delay-Dur)} & ,T\geq Delay+Dur\end{array}\right\} \tag{21}$$

References

1. Graham MM. Physiologic smoothing of blood time-activity curves for PET data analysis. *J. Nucl. Med.* 1997; 38: 1161-1168.
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.