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

![Graham’s compartmental model extended with compartments for a metabolite.](image)
Table B1-1. Descriptions of the model parameters.

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

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

\[
\begin{align*}
\text{Input}(t) &= \begin{cases} 
0 & , t < \text{Delay} \\
H \times e^{-k(t-Delay)} & , t \geq \text{Delay}
\end{cases} 
\quad (1) \\
\text{Input}(t) &= \begin{cases} 
0 & , t < \text{Delay} \\
H \times \left(1 - e^{-k(t-Delay)}\right) & , \text{Delay} \geq t > \text{Delay} + Dur \\
H \times e^{-k(t-Delay-Dur)} & , t \geq \text{Delay} + Dur
\end{cases} 
\end{align*}
\]

Integral of input

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

\[
\int_{0}^{T} \text{Input}(t) dt = \begin{cases} 
0 & , T < \text{Delay} \\
H \frac{k}{k} \left(1 - e^{-k(T-Delay)}\right) & , T \geq \text{Delay}
\end{cases} 
\quad (3)
\]

and for infusion integral:

\[
\int_{0}^{T} \text{Input}(t) dt = \begin{cases} 
0 & , T < \text{Delay} \\
H(T - \text{Delay}) - H \frac{k}{k} \left(1 - e^{-k(T-Delay)}\right) & , \text{Delay} \leq T < \text{Delay} + Dur \\
H \times \text{Dur} - H \frac{k}{k} \left(1 - e^{-k(T-Delay-Dur)}\right) e^{-k(T-Delay-Dur)} & , T \geq \text{Delay} + Dur
\end{cases} 
\quad (4)
\]

Differential equations for the concentrations in model compartments

\[
\begin{align*}
V_p \frac{dC_p^{\text{a}}(t)}{dt} &= \text{Input}(t) - \left(PS_1^{\text{a}} + GFR\right) \times C_p^{\text{a}}(t) + PS_1^{\text{a}} \times C_i^{\text{a}}(t) 
\quad (5) \\
V_i \frac{dC_i^{\text{a}}(t)}{dt} &= PS_1^{\text{a}} \times C_p^{\text{a}}(t) + PS_2^{\text{a}} \times C_i^{\text{a}}(t) - \left(PS_1^{\text{a}} + PS_2^{\text{a}} + MR_1\right) \times C_i^{\text{a}}(t) 
\quad (6) \\
V_i \frac{dC_i^{\text{m}}(t)}{dt} &= PS_2^{\text{a}} \times C_i^{\text{a}}(t) - \left(PS_2^{\text{a}} + MR_2\right) \times C_i^{\text{a}}(t) 
\quad (7) \\
V_p \frac{dC_p^{\text{m}}(t)}{dt} &= PS_1^{\text{m}} \times C_i^{\text{m}}(t) - \left(PS_1^{\text{m}} + GFR\right) \times C_p^{\text{m}}(t) 
\quad (8) \\
V_i \frac{dC_i^{\text{m}}(t)}{dt} &= MR_1 \times C_i^{\text{a}}(t) + PS_1^{\text{m}} \times C_p^{\text{m}}(t) + PS_2^{\text{m}} \times C_i^{\text{m}}(t) - \left(PS_1^{\text{m}} + PS_2^{\text{m}}\right) \times C_i^{\text{m}}(t) 
\quad (9) \\
V_i \frac{dC_i^{\text{m}}(t)}{dt} &= MR_2 \times C_i^{\text{a}}(t) + PS_2^{\text{m}} \times C_i^{\text{m}}(t) - PS_2^{\text{m}} \times C_i^{\text{m}}(t) 
\quad (10)
\end{align*}
\]
Solving differential equations

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

\[
C^a_p(T) = \frac{PS^a_2 \int_0^T C^a_i(t)dt - \left(PS^a_2 + MR^a_2\right) \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right]}{V^a_i + \frac{\Delta t}{2} \left(PS^a_2 + MR^a_2\right)}
\]  
(11)

\[
\int_0^T C^a_i(t)dt = \frac{PS^a_2 \int_0^T C^a_i(t)dt + V^a_i \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right]}{V^a_i + \frac{\Delta t}{2} \left(PS^a_2 + MR^a_2\right)}
\]  
(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:

\[
C^a_i(T) = \frac{PS^a_i \int_0^T C^a_p(t)dt + A V^a_i \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right] - \left(PS^a_i + MR^a_i + PS^a_2 \left(1 - \frac{\Delta t}{2} A\right)\right) \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right]}{V^a_i + \frac{\Delta t}{2} \left(PS^a_i + MR^a_i + PS^a_2 \left(1 - \frac{\Delta t}{2} A\right)\right)}
\]  
(13)

\[
\int_0^T C^a_i(t)dt = \frac{PS^a_i \int_0^T C^a_p(t)dt + A V^a_i \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right] + V^a_i \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right]}{V^a_i + \frac{\Delta t}{2} \left(PS^a_i + MR^a_i + PS^a_2 \left(1 - \frac{\Delta t}{2} A\right)\right)}
\]  
(14)

, where \( A = PS^a_2/(V^a_i + (\Delta t/2) \cdot (PS^a_2 + MR^a_2)) \). Integration of Eq. (5), substitution of Eq. (14) and solving gives the equation for the concentration of parent tracer in plasma volume:

\[
C^a_p(T) = \frac{\int_0^T Input(t)dt - \left(GFR^a + PS^a_i \left(1 - \frac{\Delta t}{2} B\right)\right) \left[\int_0^{T-\Delta t} C^a_p(t)dt + \frac{\Delta t}{2} C^a_p(t)\right] + A B V^a_i \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right] + B V^a_i \left[\int_0^{T-\Delta t} C^a_i(t)dt + \frac{\Delta t}{2} C^a_i(t)\right]}{V^a_p + \frac{\Delta t}{2} \left(GFR^a + PS^a_i \left(1 - \frac{\Delta t}{2} B\right)\right)}
\]  
(15)

, where \( B = PS^a_1/(V^a_p + (\Delta t/2) \cdot (PS^a_1 + MR^a_1 + PS^a_2 \cdot (1 - (\Delta t/2) \cdot A))) \).
Integration of Eq. (10) and solving gives equations for the concentration of labeled metabolite in tissue volume and its integral:

\[
C_i^m(T) = \frac{MR\int_0^T C_i^a(t)dt + PS_i^m\int_0^T C_i^m(t)dt - \frac{\Delta t}{2} \left[ \int_0^T C_i^m(t)dt + \frac{\Delta t}{2} C_i^m(T - \Delta t) \right]}{V_i^m + \frac{\Delta t}{2} PS_i^m}
\]  

(16)

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

(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:

\[
C_i^m(T) = \frac{MR_1\int_0^T C_i^a(t)dt + PS_1^m\int_0^T C_p^m(t)dt + D MR_2\int_0^T C_i^a(t)dt}{V_i^m + \frac{\Delta t}{2} \left( PS_1^m + PS_2^m \left( 1 - \frac{\Delta t}{2} D \right) \right)}
\]  

(18)

\[
\int_0^T C_i^m(t)dt = \frac{MR_1\frac{\Delta t}{2} \left[ \int_0^T C_i^a(t)dt + \frac{\Delta t}{2} C_i^a(T - \Delta t) \right] + D V_i^m \left[ \int_0^T C_i^m(t)dt + \frac{\Delta t}{2} C_i^m(T - \Delta t) \right]}{V_i^m + \frac{\Delta t}{2} \left( PS_1^m + PS_2^m \left( 1 - \frac{\Delta t}{2} D \right) \right)}
\]  

(19)

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

\[
C_p^m(T) = \frac{E MR_1\frac{\Delta t}{2} \left[ \int_0^T C_i^a(t)dt \right] + D E MR_2 \left( \frac{\Delta t}{2} \right)^2 \left[ \int_0^T C_i^a(t)dt \right] - \left( GFR^m + PS_1^m \left( 1 - \frac{\Delta t}{2} E \right) \right) \left[ \int_0^T C_p^m(t)dt + \frac{\Delta t}{2} C_p^m(T - \Delta t) \right] + D E V_i^m \left[ \int_0^T C_i^m(t)dt + \frac{\Delta t}{2} C_i^m(T - \Delta t) \right] + E V_i^m \left[ \int_0^T C_i^m(t)dt + \frac{\Delta t}{2} C_i^m(T - \Delta t) \right]}{V_p^m + \frac{\Delta t}{2} \left( GFR^m + PS_1^m \left( 1 - \frac{\Delta t}{2} E \right) \right)}
\]  

(20)
\[ E = \frac{PS_1^m}{V_i^m + (\Delta t/2) \cdot (PS_1^m + PS_2^m \cdot (1 - (\Delta t/2) \cdot D))} \]

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