## Mathematical equations for compartmental models

Below are rate equations associated to four different compartment models that can be used to approximate the quantities of a compound dosed to a mammalian body; these models being referred to in the associated article.

## **Intravenous 1-compartment model**

Intravenous dose directly into compartment B that represents the body and from which the compound is eliminated according to the rate constant  $k_4$ .

Equation 1:

$$\frac{dx_B}{dt} = -k_4 x_B$$

Equation 2:

$$x_B = x_B^0 e^{-k_4 t}$$

where  $x_B^0$  equals the intravenous dose (mg) and  $x_B$  the quantity (mg) of the compound in compartment B at a particular time point, *t*. See below for details on  $k_4$ .

## **Intravenous 2-compartment model**

Intravenous dose directly into compartment B that represents the central compartment of the body and from which compound is eliminated according to the rate constant  $k_4$ . Compound in compartment B can also distribute into and out of compartment C that represents the peripheral compartment of the body according to the rate constants  $k_2$  and  $k_3$ , respectively.

Equation 3:

$$\frac{dx_B}{dt} = -k_2 x_B + k_3 x_C - k_4 x_B$$

Equation 4:

$$x_B = \frac{x_B^0}{\beta - \alpha} \left[ (k_3 - \alpha)e^{-\alpha t} - (k_3 - \beta)e^{-\beta t} \right]$$

Equation 5:

$$\frac{dx_C}{dt} = k_2 x_B - k_3 x_C$$

Equation 6:

$$x_C = \frac{k_2 x_B^0}{\beta - \alpha} \left[ e^{-\alpha t} - e^{-\beta t} \right]$$

where  $x_B^0$  equals the intravenous dose (mg) and  $x_B$  and  $x_C$  are the quantities (mg) of the compound in compartment B and C, respectively, at a particular time point, *t*. See below for details on  $\alpha$ ,  $\beta$ ,  $k_2$  and  $k_3$ .

## **Oral 1-compartment model**

Extravascular dose into compartment A that represents the small intestines and from which compound is absorbed into compartment B according to the rate constant  $k_1$ . Compartment B represents the body from which compound is eliminated according to the rate constant  $k_4$ . Absorption from compartment A occurs during an absorption window during which the compartment could be:

- (i) saturated throughout,
- (ii) saturated at the beginning becoming unsaturated,
- (iii) unsaturated throughout.

Different equations apply depending on the above absorption scenarios and time point during the simulation. Note, at the end of the absorption window only elimination occurs and different equations also apply.

## Equations to use for time points when absorption can occur and compartment A is saturated

Equation 7:

$$\frac{dx_A}{dt} = -z$$

Equation 8:

$$\frac{dx_B}{dt} = zF_h - k_4 x_B$$

Equation 10:

$$x_B = \frac{zF_h}{k_4} (1 - e^{-k_4 t})$$

where  $x_A^0$  equals the oral dose (mg) and  $x_A$  and  $x_B$  are the quantities (mg) of the compound in compartment A and B, respectively, at a particular time point, *t*. See below for details on *z*,  $F_h$  and  $k_4$ .

$$x_A = x_A^0 - zt$$

Equations to use for time points when absorption can occur and compartment A is unsaturated

Equation 11:

$$\frac{dx_A}{dt} = -k_1 x_A$$

Equation 12:

$$x_A = x_A^0 e^{-k_1 t}$$

Equation 13:

$$\frac{dx_B}{dt} = F_h k_1 x_A - k_4 x_B$$

Equation 14:

$$x_B = \frac{F_h k_1 x_A^0}{k_4 - k_1} (e^{-k_1 t} - e^{-k_4 t}) + x_B^0 e^{-k_4 t}$$

where  $x_A^0$  equals the oral dose (mg) and  $x_A$  and  $x_B$  are the quantities (mg) of the compound in compartment A and B, respectively, at a particular time point, *t*. See below for details on  $F_h$ ,  $k_1$  and  $k_4$ . If throughout the absorption window compartment A was unsaturated then  $x_B^0$  is zero otherwise it is given by Equation 10 at the time point corresponding to the transition from a saturated to unsaturated state with respect to compartment A.

#### Equations to use for time points when absorption has ceased

Equation 15:

$$\frac{dx_B}{dt} = -k_4 x_B$$

Equation 16:

 $x_B = x_B^0 e^{-k_4 t}$ 

where  $x_B$  is the quantity (mg) of the compound in compartment B at a particular time point, *t*. Depending on the saturation state of compartment A at the end of the absorption window,  $x_B^0$  is given by Equation 10 or 14 at the time point corresponding to end of the absorption window. See below for details on  $k_4$ .

## **Oral 2-compartment**

Extravascular dose into compartment A that represents the small intestines and from which compound is absorbed into compartment B according to the rate constant  $k_1$ . Compartment B represents the body from which compound is eliminated according to the rate constant  $k_4$ . Compound in compartment B can also distribute into and out of compartment C that

represents the peripheral compartment of the body according to the rate constants  $k_2$  and  $k_3$ , respectively. Absorption from compartment A occurs during an absorption window during which the compartment could be:

- (i) saturated throughout,
- (ii) saturated at the beginning becoming unsaturated,
- (iii) unsaturated throughout.

Different equations apply depending on the above absorption scenarios and time point during the simulation. Note, at the end of the absorption window only elimination occurs and different equations also apply.

# Equations to use for time points when absorption can occur and compartment A is saturated

Equation 17:

$$\frac{dx_A}{dt} = -z$$

Equation 18:

$$x_A = x_A^0 - zt$$

Equation 19:

$$\frac{dx_B}{dt} = zF_h - k_2x_B + k_3x_C - k_4x_B$$

Equation 20:

$$x_B = zF_h \left[ \frac{k_3}{\alpha\beta} - \frac{(k_3 - \alpha)e^{-\alpha t}}{\alpha(\beta - \alpha)} + \frac{(k_3 - \beta)e^{-\beta t}}{\beta(\beta - \alpha)} \right]$$

Equation 21:

$$\frac{dx_C}{dt} = k_2 x_B - k_3 x_C$$

Equation 22:

$$x_{C} = zF_{h}k_{2}\left[\frac{1}{\alpha\beta} - \frac{e^{-\alpha t}}{\alpha(\beta - \alpha)} + \frac{e^{-\beta t}}{\beta(\beta - \alpha)}\right]$$

where  $x_A^0$  equals the oral dose (mg) and  $x_A$ ,  $x_B$  and  $x_C$  are the quantities (mg) of the compound in compartment A, B and C, respectively, at a particular time point, *t*. See below for details on *z*,  $F_h$ ,  $\alpha$ ,  $\beta$ ,  $k_2$  and  $k_3$ .

Equations to use for time points when absorption can occur and compartment A is unsaturated

Equation 23:

$$\frac{dx_A}{dt} = -k_1 x_A$$

Equation 24:

$$x_A = x_A^0 e^{-k_1 t}$$

Equation 25:

$$\frac{dx_B}{dt} = F_h k_1 x_A - k_2 x_B + k_3 x_C - k_4 x_B$$

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Equation 26:

$$\begin{aligned} x_B &= F_h k_1 x_A^0 \left[ \frac{(k_3 - k_1)e^{-k_1 t}}{(\alpha - k_1)(\beta - k_1)} - \frac{(k_3 - \alpha)e^{-\alpha t}}{(\alpha - k_1)(\beta - \alpha)} + \frac{(k_3 - \beta)e^{-\beta t}}{(\beta - k_1)(\beta - \alpha)} \right] \\ &+ \frac{x_B^0}{\beta - \alpha} \left[ (k_3 - \alpha)e^{-\alpha t} - (k_3 - \beta)e^{-\beta t} \right] + \frac{k_3 x_C^0}{\beta - \alpha} \left( e^{-\alpha t} - e^{-\beta t} \right) \end{aligned}$$

Equation 27:

$$\frac{dx_C}{dt} = k_2 x_B - k_3 x_C$$

Equation 28:

$$\begin{aligned} x_{C} &= \frac{k_{2} x_{B}^{0}}{\beta - \alpha} \left( e^{-\alpha t} - e^{-\beta t} \right) + x_{C}^{0} e^{-k_{3} t} \\ &- k_{2} k_{3} x_{C}^{0} \left[ \frac{(\beta - \alpha) e^{-k_{3} t} + (k_{3} - \beta) e^{-\alpha t} + (\alpha - k_{3}) e^{-\beta t}}{(\alpha - k_{3})(\beta - \alpha)(k_{3} - \beta)} \right] \\ &- F_{h} k_{1} k_{2} x_{A}^{0} \left[ \frac{(\beta - \alpha) e^{-k_{1} t} + (k_{1} - \beta) e^{-\alpha t} + (\alpha - k_{1}) e^{-\beta t}}{(\alpha - k_{1})(\beta - \alpha)(k_{1} - \beta)} \right] \end{aligned}$$

where  $x_A^0$  equals the oral dose (mg) and  $x_A$ ,  $x_B$  and  $x_C$  are the quantities (mg) of the compound in compartment A, B and C, respectively, at a particular time point, *t*. See below for details on  $F_h$ ,  $\alpha$ ,  $\beta$ ,  $k_1$ ,  $k_2$  and  $k_3$ . If throughout the absorption window compartment A was unsaturated then  $x_B^0$  and  $x_C^0$  are zero otherwise they are given by Equations 20 and 22, respectively, at the time point corresponding to the transition from a saturated to unsaturated state with respect to compartment A.

#### Equations to use for time points when absorption has ceased

Equation 29:

$$\frac{dx_B}{dt} = -k_2 x_B + k_3 x_C - k_4 x_B$$

Equation 30:

$$x_B = \frac{k_3 x_C^0}{\beta - \alpha} \left( e^{-\alpha t} - e^{-\beta t} \right) + \frac{x_B^0}{\beta - \alpha} \left[ (k_3 - \alpha) e^{-\alpha t} - (k_3 - \beta) e^{-\beta t} \right]$$

Equation 31:

$$\frac{dx_C}{dt} = k_2 x_B - k_3 x_C$$

Equation 32:

$$\begin{aligned} x_{C} &= x_{C}^{0} e^{-k_{3}t} + \frac{k_{2} x_{B}^{0}}{\beta - \alpha} \left( e^{-\alpha t} - e^{-\beta t} \right) \\ &- k_{2} k_{3} x_{C}^{0} \left[ \frac{(\beta - \alpha) e^{-k_{3}t} + (k_{3} - \beta) e^{-\alpha t} + (\alpha - k_{3}) e^{-\beta t}}{(\alpha - k_{3})(\beta - \alpha)(k_{3} - \beta)} \right] \end{aligned}$$

where  $x_B$  and  $x_C$  are the quantities (mg) of the compound in compartment B and C, respectively, at a particular time point, *t*. See below for details on  $\alpha$ ,  $\beta$ ,  $k_2$  and  $k_3$ . Depending on the saturation state of compartment A at the end of the absorption window,  $x_B^0$ is given by Equation 20 or 26 at the time point corresponding to end of the absorption window. Similarly, depending on the saturation state of compartment A at the end of the absorption window,  $x_C^0$  is given by Equation 22 or 28 at the time point corresponding to end of the absorption window.

### **Additional terms**

#### Saturated absorption rate (z):

Equation 33:

$$z = k_1 \cdot solubility_{pH6.5} \cdot mwt \cdot V_{intestinal}$$

where *solubility*<sub>*pH6.5*</sub> (mol L<sup>-1</sup>) is a compound's aqueous solubility at pH 6.5, *mwt* is the compound's molecular weight and  $V_{intestinal}$  is the intestinal fluid volume (80 mL).

#### Fraction escaping first pass metabolism $(F_h)$ :

Equation 34:

$$F_h = 1 - E_h = 1 - \frac{Cl}{Q_h}$$

where  $E_h$  is the compound's hepatic extraction ratio, Cl is the compound's *in vivo* clearance (L min<sup>-1</sup>) and  $Q_h$  is the liver blood flow (L min<sup>-1</sup>).

#### The $\alpha$ and $\beta$ terms:

The following two equations relate the  $\alpha$  and  $\beta$  terms to  $k_2$ ,  $k_3$  and  $k_4$ :

Equation 35:

$$\alpha + \beta = k_2 + k_3 + k_4$$

Equation 36:

$$\alpha\beta = k_3k_4$$

#### Rate constant: $k_1$ (min<sup>-1</sup>)

See the associated article for details on calculating  $k_1$ .

### Rate constant: $k_4$ (min<sup>-1</sup>)

From the perspective of a 1-compartment model for the body,  $k_4$  can be defined as: Equation 37:

$$k_4 = \frac{Cl}{V_{ss}}$$

where  $V_{ss}$  is the compound's steady state volume of distribution (L).

From the perspective of a 2-compartment model for the body (*i.e.*, central and peripheral compartment),  $k_4$  can be defined as:

Equation 38:

$$k_4 = \frac{Cl}{V_{central}}$$

where  $V_{central}$  is the compound's initial dilution volume (L).

## Rate constants: $k_2$ (min<sup>-1</sup>) and $k_3$ (min<sup>-1</sup>)

From the perspective of a 2-compartment model for the body (*i.e.*, central and peripheral compartment), *Cl* can be defined as:

Equation 39:

$$Cl = \beta V_{terminal}$$

where  $V_{terminal}$  is the compound's terminal volume of distribution (L).

Defining p as the ratio of  $V_{terminal}$  to  $V_{ss}$ : Equation 40:

$$\frac{V_{terminal}}{V_{ss}} = p$$

where  $p \ge 1$ .

Substituting *p* into Equation 39 and rearranging gives: Equation 41:

$$\beta = \frac{Cl}{pV_{ss}}$$

Furthermore, 
$$V_{ss}$$
 can be defined as:

Equation 42:

$$V_{ss} = V_{central} \left( 1 + \frac{k_2}{k_3} \right)$$

Equation 42 can be rearranged to give:

Equation 43:

$$\frac{k_2}{k_3} = \frac{V_{ss}}{V_{central}} - 1 = q$$

Equations 35 and 36 can be combine to form quadratic equations whose solutions are given by:

Equation 44:

$$\alpha = \frac{1}{2} \Big[ (k_2 + k_3 + k_4) + \sqrt{(k_2 + k_3 + k_4)^2 - 4k_3k_4} \Big]$$

Equation 45:

$$\beta = \frac{1}{2} \Big[ (k_2 + k_3 + k_4) - \sqrt{(k_2 + k_3 + k_4)^2 - 4k_3k_4} \Big]$$

Rearranging Equation 43 and substituting into Equation 45 and subsequently rearranging gives:

Equation 46:

$$k_3 = \frac{\left(\beta - \frac{\beta^2}{k_4}\right)}{\left[1 - \frac{\beta(1+q)}{k_4}\right]}$$

Based upon Equation 43, Equation 46 can be rearranged to: Equation 47:

$$k_{3} = \frac{\left(\beta - \frac{\beta^{2}}{k_{4}}\right)}{\left[1 - \frac{\beta\left(\frac{V_{ss}}{V_{central}}\right)}{k_{4}}\right]}$$

Equations 38, 41 and 47 can be combined along with a compound's Cl,  $V_{central}$ ,  $V_{ss}$  and  $V_{terminal}$  to calculate  $k_3$ . Subsequently,  $k_2$  can be determined by rearranging and solving Equation 43.