Mathematical Expressions of the Pharmacokinetic and Pharmacodynamic Models implemented in the Monolix software

Julie Bertrand and France Mentré

INSERM U738, Paris Diderot University

Programmers : Marc Lavielle, Hector Mesa and Kaelig Chatel (INRIA)

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Contents

Chapter 1

Pharmacokinetic models

The equations in the ensuing chapter describe the pharmacokinetic models implemented in the Monolix software. The presentation of the models is organised as follows:

- First level: number of compartment
  - One compartment
  - Two compartments
  - Three compartments
- Second level: route of administration
  - IV bolus
  - Infusion
  - First order absorption
  - Zero order absorption
- Third level: elimination process
  - Linear
  - Michaelis-Menten
- Fourth level: existence of a lag time for first and zero order absorption only

- Last level: administration profile

  The equations express the concentration $C(t)$ in the central compartment at a time t after the last drug administration.

  - Single dose: at time t after dose D given at time t_D $(t \geq t_D)$
  - Multiples doses: at time t after n doses D_i $(i = 1, ...n)$ given at time t_{D_i} $(t \geq t_{D_n})$
  - Steady state: at a time t after dose D given at time t_D after repeated administration of dose D given at interval τ $(t \geq t_D)$ *(only for linear elimination)*

NB1: For infusion, the duration of infusion is $Tinf$ for single dose and $Tinf_i$ $(i = 1, ...n)$ for multiple doses; D and D_i are the total doses administrated.

For multiple doses, the delay between successive doses is supposed to be greater than infusion duration and absorption duration ($t_{D_{i+1}} - t_{D_i} > Tinf_i$ and $t_{D_{i+1}} - t_{D_i} > Tk_0$).

For steady state, the interval τ is supposed to be greater than infusion duration and absorption duration ($\tau > Tinf$ and $\tau > Tk_0$).

NB2: For models with 1 and 2 compartments, equations $C(t)$ express concentration in the central compartment at a time t after drug administration and are in the PK library (Appendix I). PK/PD analysis, with intermediate response models, can use concentration $C(t)$ in the central compartment but alternatively concentration $C_e(t)$ in the effect compartment. In that case a model in library $PKe0$ (Appendix II) should be used.

There is an additionnal parameter to estimate, k_{e0} the equilibrium rate constant between central and effect compartment.

For each model the equation for $C_e(t)$ is given after the corresponding one for $C(t)$.

1.1 One compartment models

Parameters

- V = volume of distribution
- k = elimination rate constant
- Cl = clearance of elimination
- V_m = maximum elimination rate (in amount per time unit)
- K_m = Michaelis-Menten constant (in concentration unit)
- k_a = absorption rate constant
- $Tlag$ = lag time
- Tk_0 = absorption duration for zero order absorption

NB: V and Cl are apparent volume and oral clearance for extra-vascular administration.

Parameterisation

There are two parameterisations for one compartment models, (V and k) or (V and Cl). The equations are given for the first parameterisation (V, k). The equations for the second parameterisation (V, Cl) are derived using $k = \frac{Cl}{V}$.

1.1.1 IV bolus

1.1.1.1 Linear elimination

- single dose

$$C(t) = \frac{D}{V} e^{-k(t-t_D)} \tag{1.1}$$

$$C_e(t) = \frac{D}{V} \frac{k_{e0}}{(k_{e0}-k)} \left(e^{-k(t-t_D)} - e^{-k_{e0}(t-t_D)}\right)$$

- multiple doses

$$C(t) = \sum_{i=1}^{n} \frac{D_i}{V} e^{-k\left(t-t_{D_i}\right)} \tag{1.2}$$

$$C_e(t) = \sum_{i=1}^{n} \frac{D_i}{V} \frac{k_{e0}}{(k_{e0}-k)} \left(e^{-k\left(t-t_{D_i}\right)} - e^{-k_{e0}\left(t-t_{D_i}\right)}\right)$$

- steady state

$$C(t) = \frac{D}{V} \frac{e^{-k(t-t_D)}}{1-e^{-k\tau}} \tag{1.3}$$

$$C_e(t) = \frac{D}{V} \frac{k_{e0}}{(k_{e0}-k)} \left(\frac{e^{-k(t-t_D)}}{1-e^{-k\tau}} - \frac{e^{-k_{e0}(t-t_D)}}{1-e^{-k_{e0}\tau}}\right)$$

Equations 1.1 to 1.3 correspond to models n°1: bolus_1cpt_Vk and n°2: bolus_1cpt_VCl.

1.1.1.2 Michaelis Menten elimination

- single dose

$$\text{Initial conditions: } \begin{cases} C(t) & = 0 \text{ for } t < t_D \\ C_e(t) & = 0 \text{ for } t \leq t_D \\ C(t_D) & = \frac{D}{V} \end{cases}$$

$$\frac{dC}{dt} = -\frac{\frac{V_m}{V} \times C}{K_m + C} \tag{1.4}$$

$$\frac{dC_e}{dt} = k_{e0}(C - C_e)$$

- multiple doses

$C^{(n)}(t)$ is the concentration after the n^{th} dose.

$$\begin{aligned} C(t) &= 0 \text{ for } t < t_{D_1} \\ C_e(t) &= 0 \text{ for } t \leq t_{D_1} \\ C(t_{D_1}) &= C^{(1)}(t_{D_1}) = \frac{D_1}{V} \\ C(t_{D_n}) &= C^{(n)}(t_{D_n}) = C^{(n-1)}(t_{D_n}) + \frac{D_n}{V} \\ \text{and when } t \neq t_{D_i}\text{: } & \begin{cases} \frac{dC}{dt} = -\frac{\frac{V_m}{V} \times C}{K_{m+C}} \\ \frac{dC_e}{dt} = k_{e0}(C - C_e) \end{cases} \end{aligned} \tag{1.5}$$

Equations 1.4 and 1.5 correspond to model n°3: bolus_1cpt_VVmKm.

1.1.2 IV infusion

1.1.2.1 Linear elimination

- single dose

$$C(t) = \begin{cases} \frac{D}{Tinf} \frac{1}{kV} \left(1 - e^{-k(t-t_D)}\right) & \text{if } t - t_D \leq Tinf, \\ \frac{D}{Tinf} \frac{1}{kV} \left(1 - e^{-kTinf}\right) e^{-k(t-t_D-Tinf)} & \text{if not.} \end{cases} \tag{1.6}$$

$$C_e(t) = \begin{cases} \frac{D}{Tinf} \frac{1}{kV(k_{e0}-k)} \left[k_{e0}\left(1 - e^{-k(t-t_D)}\right) - k\left(1 - e^{-k_{e0}(t-t_D)}\right)\right] & \text{if } t - t_D \leq Tinf, \\ \frac{D}{Tinf} \frac{1}{kV(k_{e0}-k)} \left[\begin{array}{l} k_{e0}\left(1 - e^{-kTinf}\right) e^{-k(t-t_D-Tinf)} \\ -\, k\left(1 - e^{-k_{e0}Tinf}\right) e^{-k_{e0}(t-t_D-Tinf)} \end{array}\right] & \text{if not.} \end{cases}$$

- multiple doses

$$C(t) = \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{Tinf_i} \frac{1}{kV} \left(1 - e^{-kTinf_i}\right) e^{-k\left(t-t_{D_i}-Tinf_i\right)} \\ \qquad + \frac{D_n}{Tinf_n} \frac{1}{kV} \left(1 - e^{-k(t-t_{D_n})}\right) & \text{if } t - t_{D_n} \leq Tinf_n, \\ \sum_{i=1}^{n} \frac{D_i}{Tinf_i} \frac{1}{kV} \left(1 - e^{-kTinf_i}\right) e^{-k\left(t-t_{D_i}-Tinf_i\right)} & \text{if not.} \end{cases} \tag{1.7}$$

$$C_e(t) = \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{Tinf_i} \frac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}(1-e^{-kTinf_i})e^{-k(t-t_{D_i}-Tinf_i)} \\ -k(1-e^{-k_{e0}Tinf_i})e^{-k_{e0}(t-t_{D_i}-Tinf_i)} \end{bmatrix} \\ \qquad + \frac{D_n}{Tinf_n} \frac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\left(1-e^{-k(t-t_{D_n})}\right) \\ -k\left(1-e^{-k_{e0}(t-t_{D_n})}\right) \end{bmatrix} & \text{if } t-t_{D_n} \leq Tinf_n, \\ \sum_{i=1}^{n} \frac{D_i}{Tinf_i} \frac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\left(1-e^{-kTinf_i}\right) e^{-k\left(t-t_{D_i}-Tinf_i\right)} \\ -k\left(1-e^{-k_{e0}Tinf_i}\right) e^{-k_{e0}\left(t-t_{D_i}-Tinf_i\right)} \end{bmatrix} & \text{if not.} \end{cases}$$

- steady state

$$C(t) = \begin{cases} \frac{D}{Tinf} \frac{1}{kV} \left[\left(1-e^{-k(t-t_D)}\right) + e^{-k\tau} \frac{\left(1-e^{-kTinf}\right) e^{-k(t-t_D-Tinf)}}{1-e^{-k\tau}} \right] & \text{if } (t-t_D) \leq Tinf, \\ \frac{D}{Tinf} \frac{1}{kV} \frac{\left(1-e^{-kTinf}\right) e^{-k(t-t_D-Tinf)}}{1-e^{-k\tau}} & \text{if not.} \end{cases} \tag{1.8}$$

$$C_e(t) = \begin{cases} \frac{D}{Tinf} \frac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0} \left[\left(1-e^{-k(t-t_D)}\right) + e^{-k\tau} \frac{\left(1-e^{-kTinf}\right) e^{-k(t-t_D-Tinf)}}{1-e^{-k\tau}} \right] \\ -k \left[\left(1-e^{-k_{e0}(t-t_D)}\right) + e^{-k_{e0}\tau} \frac{\left(1-e^{-k_{e0}Tinf}\right) e^{-k_{e0}(t-t_D-Tinf)}}{1-e^{-k_{e0}\tau}} \right] \end{bmatrix} & \text{if } t-t_D \leq Tinf, \\ \frac{D}{Tinf} \frac{1}{kV(k_{e0}-k)} \left[k_{e0} \frac{\left(1-e^{-kTinf}\right) e^{-k(t-t_D-Tinf)}}{1-e^{-k\tau}} - k \frac{\left(1-e^{-k_{e0}Tinf}\right) e^{-k_{e0}(t-t_D-Tinf)}}{1-e^{-k_{e0}\tau}} \right] & \text{if not.} \end{cases}$$

Equations 1.6 to 1.8 correspond to models n°4: infusion_1cpt_Vk and n°5: infusion_1cpt_VCl.

1.1.2.2 Michaelis Menten elimination

- single dose

$$\begin{aligned} \text{Initial condition: } & C(t) = 0 \text{ for } t < t_D \\ & C_e(t) = 0 \text{ for } t < t_D \\ \frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\ \frac{dC_e}{dt} &= k_{e0}\left(C - C_e\right) \\ input(t) &= \begin{cases} \frac{D}{Tinf} \frac{1}{V} & \text{if } 0 \leq t - t_D \leq Tinf \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.9}$$

- multiple doses

$$
\begin{aligned}
\text{Initial condition: } & C(t) = 0 \text{ for } t < t_{D_1} \\
& C_e(t) = 0 \text{ for } t < t_{D_1} \\
\frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\
\frac{dC_e}{dt} &= k_{e0}\left(C - C_e\right) \\
input\left(t\right) &= \begin{cases} \dfrac{D_i}{Tinf_i}\dfrac{1}{V} & \text{if } 0 \leq t - t_{D_i} \leq Tinf_i, \\ 0 & \text{if not.} \end{cases}
\end{aligned}
\tag{1.10}
$$

Equations 1.9 and 1.10 correspond to model n°6: infusion_1cpt_VVmKm.

1.1.3 First order absorption

1.1.3.1 Linear elimination

- in absence of a lag time
  - single dose

$$
C\left(t\right) = \frac{D}{V}\frac{k_a}{k_a - k}\left(e^{-k(t-t_D)} - e^{-k_a(t-t_D)}\right) \tag{1.11}
$$

$$
C_e\left(t\right) = \frac{Dk_ak_{e0}}{V}\left(\frac{e^{-k_a(t-t_D)}}{(k-k_a)(k_{e0}-k_a)} + \frac{e^{-k(t-t_D)}}{(k_a-k)(k_{e0}-k)} + \frac{e^{-k_{e0}(t-t_D)}}{(k_a-k_{e0})(k-k_{e0})}\right)
$$

  - multiple doses

$$
C\left(t\right) = \sum_{i=1}^{n}\frac{D_i}{V}\frac{k_a}{k_a - k}\left(e^{-k\left(t-t_{D_i}\right)} - e^{-k_a\left(t-t_{D_i}\right)}\right) \tag{1.12}
$$

$$
C_e\left(t\right) = \sum_{i=1}^{n}\frac{D_ik_ak_{e0}}{V}\left(\frac{e^{-k_a\left(t-t_{D_i}\right)}}{(k-k_a)(k_{e0}-k_a)} + \frac{e^{-k\left(t-t_{D_i}\right)}}{(k_a-k)(k_{e0}-k)} + \frac{e^{-k_{e0}\left(t-t_{D_i}\right)}}{(k_a-k_{e0})(k-k_{e0})}\right)
$$

  - steady state

$$
C\left(t\right) = \frac{D}{V}\frac{k_a}{k_a - k}\left(\frac{e^{-k(t-t_D)}}{1-e^{-k\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \tag{1.13}
$$

$$C_e(t) = \frac{Dk_a k_{e0}}{V} \begin{pmatrix} \dfrac{e^{-k_a(t-t_D)}}{(k-k_a)(k_{e0}-k_a)(1-e^{-k_a\tau})} \\ + \dfrac{e^{-k(t-t_D)}}{(k_a-k)(k_{e0}-k)(1-e^{-k\tau})} \\ + \dfrac{e^{-k_{e0}(t-t_D)}}{(k_a-k_{e0})(k-k_{e0})(1-e^{-k_{e0}\tau})} \end{pmatrix}$$

Equations 1.11 to 1.13 correspond to models n°7: oral1_1cpt_kaVk and n°8: oral1_1cpt_kaVCl.

- in presence of a lag time
  - single dose

$$C(t) = \begin{cases} 0 & \text{if } t-t_D \leq Tlag, \\ \dfrac{D}{V}\dfrac{k_a}{k_a-k}\left(e^{-k(t-t_D-Tlag)} - e^{-k_a(t-t_D-Tlag)}\right) & \text{if not.} \end{cases} \tag{1.14}$$

$$C_e(t) = \begin{cases} 0 & \text{if } t-t_D \leq Tlag, \\ \dfrac{Dk_a k_{e0}}{V} \begin{pmatrix} \dfrac{e^{-k_a(t-t_D-Tlag)}}{(k-k_a)(k_{e0}-k_a)} + \dfrac{e^{-k(t-t_D-Tlag)}}{(k_a-k)(k_{e0}-k)} \\ + \dfrac{e^{-k_{e0}(t-t_D-Tlag)}}{(k_a-k_{e0})(k-k_{e0})} \end{pmatrix} & \text{if not.} \end{cases}$$

  - multiple doses

$$C(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{V}\frac{k_a}{k_a-k}\left(e^{-k\left(t-t_{D_i}-Tlag\right)} - e^{-k_a\left(t-t_{D_i}-Tlag\right)}\right) & \text{if } t-t_{D_n} \leq Tlag, \\ \displaystyle\sum_{i=1}^{n} \frac{D_i}{V}\frac{k_a}{k_a-k}\left(e^{-k\left(t-t_{D_i}-Tlag\right)} - e^{-k_a\left(t-t_{D_i}-Tlag\right)}\right) & \text{if not.} \end{cases} \tag{1.15}$$

$$C_e(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \left[\frac{D_i k_a k_{e0}}{V} \begin{pmatrix} \dfrac{e^{-k_a\left(t-t_{D_i}-Tlag\right)}}{(k-k_a)(k_{e0}-k_a)} + \dfrac{e^{-k\left(t-t_{D_i}-Tlag\right)}}{(k_a-k)(k_{e0}-k)} \\ + \dfrac{e^{-k_{e0}\left(t-t_{D_i}-Tlag\right)}}{(k_a-k_{e0})(k-k_{e0})} \end{pmatrix} \right] & \text{if } t-t_{D_i} \leq Tlag, \\ \displaystyle\sum_{i=1}^{n} \left[\frac{D_i k_a k_{e0}}{V} \begin{pmatrix} \dfrac{e^{-k_a\left(t-t_{D_i}-Tlag\right)}}{(k-k_a)(k_{e0}-k_a)} + \dfrac{e^{-k\left(t-t_{D_i}-Tlag\right)}}{(k_a-k)(k_{e0}-k)} \\ + \dfrac{e^{-k_{e0}\left(t-t_{D_i}-Tlag\right)}}{(k_a-k_{e0})(k-k_{e0})} \end{pmatrix} \right] & \text{if not.} \end{cases}$$

– steady state

$$C(t) = \begin{cases} \frac{D}{V}\frac{k_a}{k_a-k}\left(\frac{e^{-k(t-t_D+\tau-Tlag)}}{1-e^{-k\tau}} - \frac{e^{-k_a(t-t_D+\tau-Tlag)}}{1-e^{-k_a\tau}}\right) & \text{if } t-t_D < Tlag \\ \frac{D}{V}\frac{k_a}{k_a-k}\left(\frac{e^{-k(t-t_D-Tlag)}}{1-e^{-k\tau}} - \frac{e^{-k_a(t-t_D-Tlag)}}{1-e^{-k_a\tau}}\right) & \text{if not.} \end{cases} \tag{1.16}$$

$$C_e(t) = \begin{cases} \frac{Dk_ak_{e0}}{V}\left(\begin{array}{l} \frac{e^{-k_a(t-t_D+\tau-Tlag)}}{(k-k_a)(k_{e0}-k_a)(1-e^{-k_a\tau})} \\ + \frac{e^{-k(t-t_D+\tau-Tlag)}}{(k_a-k)(k_{e0}-k)(1-e^{-k\tau})} \\ + \frac{e^{-k_{e0}(t-t_D+\tau-Tlag)}}{(k_a-k_{e0})(k-k_{e0})(1-e^{-k_{e0}\tau})} \end{array}\right) & \text{if } t-t_D < Tlag \\ \frac{Dk_ak_{e0}}{V}\left(\begin{array}{l} \frac{e^{-k_a(t-t_D-Tlag)}}{(k-k_a)(k_{e0}-k_a)(1-e^{-k_a\tau})} \\ + \frac{e^{-k(t-t_D-Tlag)}}{(k_a-k)(k_{e0}-k)(1-e^{-k\tau})} \\ + \frac{e^{-k_{e0}(t-t_D-Tlag)}}{(k_a-k_{e0})(k-k_{e0})(1-e^{-k_{e0}\tau})} \end{array}\right) & \text{if not.} \end{cases}$$

Equations 1.14 to 1.16 correspond to models n°10: oral1_1cpt_TlagkaVk and n°11: oral1_1cpt_TlagkaVCl.

1.1.3.2 Michaelis Menten elimination

- in absence of a lag time

  – single dose

$$\begin{aligned} \text{Initial condition: } C(t) &= 0 \text{ for } t < t_D \\ C_e(t) &= 0 \text{ for } t < t_D \\ \frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\ \frac{dC_e}{dt} &= k_{e0}(C - C_e) \\ input(t) &= \frac{D}{V} k_a e^{-k_a(t-t_D)} \end{aligned} \tag{1.17}$$

  – multiple doses

$$\begin{aligned} \text{Initial condition: } C(t) &= 0 \text{ for } t < t_{D_1} \\ C_e(t) &= 0 \text{ for } t < t_{D_1} \\ \frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\ \frac{dC_e}{dt} &= k_{e0}(C - C_e) \\ input(t) &= \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a\left(t-t_{D_i}\right)} \end{aligned} \tag{1.18}$$

  Equations 1.17 and 1.18 correspond to model n°9: oral1_1cpt_kaVVmKm.

- in presence of a lag time

  – single dose

$$\begin{aligned} \text{Initial condition: } C(t) &= 0 \text{ for } t < t_D \\ C_e(t) &= 0 \text{ for } t < t_D \\ \frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\ \frac{dC_e}{dt} &= k_{e0}(C - C_e) \\ input(t) &= \begin{cases} 0 & \text{if } t - t_D < Tlag, \\ \frac{D}{V} k_a e^{-k_a(t-t_D-Tlag)} & \text{if not.} \end{cases} \end{aligned} \tag{1.19}$$

– multiple doses

$$\begin{aligned}
\text{Initial condition: } & C(t) = 0 \text{ for } t < t_{D_1} \\
& C_e(t) = 0 \text{ for } t < t_{D_1} \\
\frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\
\frac{dC_e}{dt} &= k_{e0}\left(C - C_e\right) \\
input(t) &= \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{V} k_a e^{-k_a\left(t - t_{D_i} - Tlag\right)} & \text{if } t - t_{D_n} < Tlag, \\ \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a\left(t - t_{D_i} - Tlag\right)} & \text{if not.} \end{cases}
\end{aligned} \tag{1.20}$$

Equations 1.19 and 1.20 correspond to model n°12: oral1_1cpt_TlagkaVVmKm.

1.1.4 Zero order absorption

1.1.4.1 Linear elimination

- in absence of a lag time

– single dose

$$C(t) = \begin{cases} \frac{D}{Tk_0}\frac{1}{kV}\left(1 - e^{-k(t-t_D)}\right) & \text{if } t - t_D \le Tk_0, \\ \frac{D}{Tk_0}\frac{1}{kV}\left(1 - e^{-kTk_0}\right)e^{-k(t-t_D-Tk_0)} & \text{if not.} \end{cases} \tag{1.21}$$

$$C_e(t) = \begin{cases} \frac{D}{Tk_0}\frac{1}{kV(k_{e0}-k)}\left[k_{e0}\left(1 - e^{-k(t-t_D)}\right) - k\left(1 - e^{-k_{e0}(t-t_D)}\right)\right] & \text{if } t - t_D \le Tk_0, \\ \frac{D}{Tk_0}\frac{1}{kV(k_{e0}-k)}\begin{bmatrix} k_{e0}\left(1 - e^{-kTk_0}\right)e^{-k(t-t_D-Tk_0)} \\ -k\left(1 - e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tk_0)} \end{bmatrix} & \text{if not.} \end{cases}$$

– multiple doses

$$C(t) = \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{Tk_0}\frac{1}{kV}\left(1 - e^{-kTk_0}\right)e^{-k\left(t - t_{D_i} - Tk_0\right)} + \frac{D_n}{Tk_0}\frac{1}{kV}\left(1 - e^{-k(t-t_{D_n})}\right) & \text{if } t - t_{D_n} \le Tk_0, \\ \sum_{i=1}^{n} \frac{D_i}{Tk_0}\frac{1}{kV}\left(1 - e^{-kTk_0}\right)e^{-k\left(t - t_{D_i} - Tk_0\right)} & \text{if not.} \end{cases} \tag{1.22}$$

$$C_e(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{Tk_0} \frac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}(1-e^{-kTk_0})e^{-k(t-t_{D_i}-Tk_0)} \\ -k(1-e^{-k_{e0}Tk_0})e^{-k_{e0}(t-t_{D_i}-Tk_0)} \end{bmatrix} & \\ \qquad + \dfrac{D_n}{Tk_0}\dfrac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\left(1-e^{-k(t-t_{D_n})}\right) \\ -k\left(1-e^{-k_{e0}(t-t_{D_n})}\right) \end{bmatrix} & \text{if } t-t_{D_n} \leq Tk_0, \\ \displaystyle\sum_{i=1}^{n} \frac{D_i}{Tk_0} \frac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\left(1-e^{-kTk_0}\right) e^{-k\left(t-t_{D_i}-Tk_0\right)} \\ -k\left(1-e^{-k_{e0}Tk_0}\right) e^{-k_{e0}\left(t-t_{D_i}-Tk_0\right)} \end{bmatrix} & \text{if not.} \end{cases}$$

– steady state

$$C(t) = \begin{cases} \dfrac{D}{Tk_0}\dfrac{1}{kV}\left[\left(1-e^{-k(t-t_D)}\right) + e^{-k\tau}\dfrac{\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tk_0)}}{1-e^{-k\tau}}\right] & \text{if } t-t_D \leq Tk_0, \\ \dfrac{D}{Tk_0}\dfrac{1}{kV}\dfrac{\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tk_0)}}{1-e^{-k\tau}} & \text{if not.} \end{cases} \tag{1.23}$$

$$C_e(t) = \begin{cases} \dfrac{D}{Tk_0}\dfrac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\left[\left(1-e^{-k(t-t_D)}\right) + e^{-k\tau}\dfrac{\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tk_0)}}{1-e^{-k\tau}}\right] \\ -k\left[\left(1-e^{-k_{e0}(t-t_D)}\right) + e^{-k_{e0}\tau}\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tk_0)}}{1-e^{-k_{e0}\tau}}\right] \end{bmatrix} & \text{if } t-t_D \leq Tk_0, \\ \dfrac{D}{Tk_0}\dfrac{1}{kV(k_{e0}-k)}\left[k_{e0}\dfrac{\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tk_0)}}{1-e^{-k\tau}} - k\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tk_0)}}{1-e^{-k_{e0}\tau}}\right] & \text{if not.} \end{cases}$$

Equations 1.21 to 1.23 correspond to models n°13: oral0_1cpt_Tk0Vk and n°14: oral0_1cpt_Tk0VCl.

- in presence of a lag time

  – single dose

$$C(t) = \begin{cases} 0 & \text{if } t-t_D \leq Tlag, \\ \dfrac{D}{Tk_0}\dfrac{1}{kV}\left(1-e^{-k(t-t_D-Tlag)}\right) & \text{if } Tlag < t-t_D \leq Tlag+Tk_0, \\ \dfrac{D}{Tk_0}\dfrac{1}{kV}\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tlag-Tk_0)} & \text{if not.} \end{cases} \tag{1.24}$$

$$C_e(t) = \begin{cases} 0 & \text{if } t-t_D \leq Tlag, \\ \dfrac{D}{Tk_0}\dfrac{1}{kV(k_{e0}-k)}\left[k_{e0}\left(1-e^{-k(t-t_D-Tlag)}\right) - k\left(1-e^{-k_{e0}(t-t_D-Tlag)}\right)\right] & \text{if } Tlag < t-t_D \leq Tlag+Tk_0 \\ \dfrac{D}{Tk_0}\dfrac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tlag-Tk_0)} \\ -k\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tlag-Tk_0)} \end{bmatrix} & \text{if not.} \end{cases}$$

– multiple doses

$$C(t) = \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{Tk_0} \frac{1}{kV} \left(1 - e^{-kTk_0}\right) e^{-k\left(t - t_{D_i} - Tlag - Tk_0\right)} & \text{if } t - t_{D_n} \leq Tlag, \\ \sum_{i=1}^{n-1} \frac{D_i}{Tk_0} \frac{1}{kV} \left(1 - e^{-kTk_0}\right) e^{-k\left(t - t_{D_i} - Tlag - Tk_0\right)} & \text{if } Tlag < t - t_{D_n} \\ \qquad + \frac{D_n}{Tk_0} \frac{1}{kV} \left(1 - e^{-k(t - t_{D_n} - Tlag)}\right) & \qquad \leq Tlag + Tk_0, \\ \sum_{i=1}^{n} \frac{D_i}{Tk_0} \frac{1}{kV} \left(1 - e^{-kTk_0}\right) e^{-k\left(t - t_{D_i} - Tlag - Tk_0\right)} & \text{if not.} \end{cases} \tag{1.25}$$

$$C_e(t) = \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{Tk_0} \frac{1}{kV(k_{e0} - k)} \begin{bmatrix} k_{e0} \left(1 - e^{-kTk_0}\right) e^{-k\left(t - t_{D_i} - Tlag - Tk_0\right)} \\ - k \left(1 - e^{-k_{e0}Tk_0}\right) e^{-k_{e0}\left(t - t_{D_i} - Tlag - Tk_0\right)} \end{bmatrix} & \text{if } t - t_{D_n} \leq Tlag, \\ \sum_{i=1}^{n-1} \frac{D_i}{Tk_0} \frac{1}{kV(k_{e0} - k)} \begin{bmatrix} k_{e0}(1 - e^{-kTk_0}) e^{-k(t - t_{D_i} - Tlag - Tk_0)} \\ - k(1 - e^{-k_{e0}Tk_0}) e^{-k_{e0}(t - t_{D_i} - Tlag - Tk_0)} \end{bmatrix} & \text{if } Tlag < t - t_{D_n} \\ \qquad + \frac{D_n}{Tk_0} \frac{1}{kV(k_{e0} - k)} \begin{bmatrix} k_{e0} \left(1 - e^{-k\left(t - t_{D_n - Tlag}\right)}\right) \\ - k \left(1 - e^{-k_{e0}\left(t - t_{D_n - Tlag}\right)}\right) \end{bmatrix} & \qquad \leq Tlag + Tk_0, \\ \sum_{i=1}^{n} \frac{D_i}{Tk_0} \frac{1}{kV(k_{e0} - k)} \begin{bmatrix} k_{e0} \left(1 - e^{-kTk_0}\right) e^{-k\left(t - t_{D_i} - Tlag - Tk_0\right)} \\ - k \left(1 - e^{-k_{e0}Tk_0}\right) e^{-k_{e0}\left(t - t_{D_i} - Tlag - Tk_0\right)} \end{bmatrix} & \text{if not.} \end{cases}$$

– steady state

$$C(t) = \begin{cases} \frac{D}{Tk_0} \frac{1}{kV} \frac{\left(1 - e^{-kTk_0}\right) e^{-k(t - t_D + \tau - Tlag - Tk_0)}}{1 - e^{-k\tau}} & t - t_D \leq Tlag, \\ \frac{D}{Tk_0} \frac{1}{kV} \begin{bmatrix} \left(1 - e^{-k(t - t_D - Tlag)}\right) \\ + e^{-k\tau} \frac{\left(1 - e^{-kTk_0}\right) e^{-k(t - t_D - Tlag - Tk_0)}}{1 - e^{-k\tau}} \end{bmatrix} & \text{if } Tlag < t - t_D \leq Tlag + Tk_0, \\ \frac{D}{Tk_0} \frac{1}{kV} \frac{\left(1 - e^{-kTk_0}\right) e^{-k(t - t_D - Tlag - Tk_0)}}{1 - e^{-k\tau}} & \text{if not.} \end{cases} \tag{1.26}$$

$$C_e(t) = \begin{cases} \dfrac{D}{Tk_0}\dfrac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\dfrac{\left(1-e^{-kTk_0}\right)e^{-k(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-k\tau}} \\ -k\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-k_{e0}\tau}} \end{bmatrix} & t-t_D \leq Tlag, \\ \dfrac{D}{Tk_0}\dfrac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\begin{bmatrix} \left(1-e^{-k(t-t_D-Tlag)}\right) \\ +e^{-k\tau}\dfrac{\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tlag-Tk_0)}}{1-e^{-k\tau}} \end{bmatrix} \\ -k\begin{bmatrix} \left(1-e^{-k_{e0}(t-t_D-Tlag)}\right) \\ +e^{-k_{e0}\tau}\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tlag-Tk_0)}}{1-e^{-k_{e0}\tau}} \end{bmatrix} \end{bmatrix} & \text{if } Tlag < t-t_D \leq Tlag+Tk_0, \\ \dfrac{D}{Tk_0}\dfrac{1}{kV(k_{e0}-k)} \begin{bmatrix} k_{e0}\dfrac{\left(1-e^{-kTk_0}\right)e^{-k(t-t_D-Tlag-Tk_0)}}{1-e^{-k\tau}} \\ -k\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tlag-Tk_0)}}{1-e^{-k_{e0}\tau}} \end{bmatrix} & \text{if not.} \end{cases}$$

Equations 1.24 to 1.26 correspond to models n°16: oral0_1cpt_TlagTk0Vk and n°17: oral0_1cpt_TlagTk0VCl.

1.1.4.2 Michaelis Menten elimination

- in absence of a lag time
  - single dose

$$\begin{aligned} \text{Initial condition: } & C(t) = 0 \text{ for } t < t_D \\ & C_e(t) = 0 \text{ for } t < t_D \\ \frac{dC}{dt} &= -\frac{\frac{V_m}{V}\times C}{K_m + C} + input \\ \frac{dC_e}{dt} &= k_{e0}\left(C - C_e\right) \\ input(t) &= \begin{cases} \dfrac{D}{Tk_0}\dfrac{1}{V} & \text{if } 0 \leq t-t_D \leq Tk_0 \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.27}$$

– multiple doses

$$\begin{aligned}
\text{Initial condition: } & C(t) = 0 \text{ for } t < t_{D_1} \\
& C_e(t) = 0 \text{ for } t < t_{D_1} \\
\frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\
\frac{dC_e}{dt} &= k_{e0}\left(C - C_e\right) \\
input(t) &= \begin{cases} \frac{D_i}{Tk_0}\frac{1}{V} & \text{if } 0 \leq t - t_{D_i} \leq Tk_0, \\ 0 & \text{if not.} \end{cases}
\end{aligned} \tag{1.28}$$

Equations 1.27 and 1.28 correspond to model n°15: oral0_1cpt_Tk0VVmKm.

- in presence of a lag time

  – single dose

$$\begin{aligned}
\text{Initial condition: } & C(t) = 0 \text{ for } t < t_D \\
& C_e(t) = 0 \text{ for } t < t_D \\
\frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\
\frac{dC_e}{dt} &= k_{e0}\left(C - C_e\right) \\
input(t) &= \begin{cases} 0 & \text{if } 0 \leq t - t_D \leq Tlag, \\ \frac{D}{Tk_0}\frac{1}{V} & \text{if } Tlag < t - t_D \leq Tlag + Tk_0, \\ 0 & \text{if not.} \end{cases}
\end{aligned} \tag{1.29}$$

  – multiple doses

$$\begin{aligned}
\text{Initial condition: } & C(t) = 0 \text{ for } t < t_{D_1} \\
& C_e(t) = 0 \text{ for } t < t_{D_1} \\
\frac{dC}{dt} &= -\frac{\frac{V_m}{V} \times C}{K_m + C} + input \\
\frac{dC_e}{dt} &= k_{e0}\left(C - C_e\right) \\
input(t) &= \begin{cases} 0 & \text{if } 0 \leq t - t_{D_i} \leq Tlag, \\ \frac{D_i}{Tk_0}\frac{1}{V} & \text{if } Tlag < t - t_{D_i} \leq Tlag + Tk_0, \\ 0 & \text{if not.} \end{cases}
\end{aligned} \tag{1.30}$$

Equations 1.29 and 1.30 correspond to model n°18: oral0_1cpt_TlagTk0VVmKm.

1.2 Two compartments models

The two compartments model implemented in Monolix is described in figure 1.1.

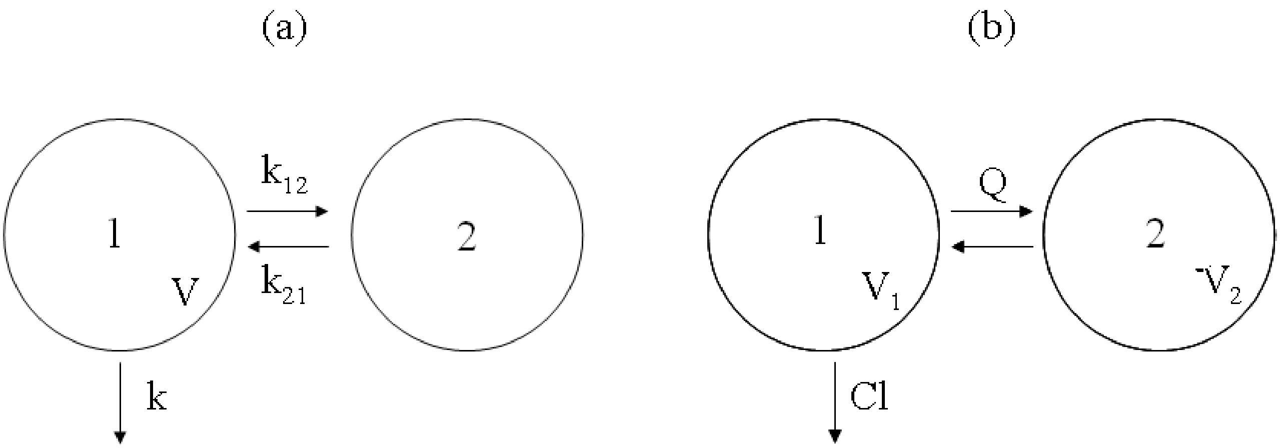

Figure 1.1: A mammillary model with two compartments, parameterized in micro-constants V, k, k_{12} and k_{21} (a) or with Cl, V_1, Q and V_2 (b)

Parameters

- $V = V_1$ = volume of distribution of first compartment
- k = elimination rate constant
- Cl = clearance of elimination
- V_m = maximum elimination rate (amount per time unit)
- K_m = Michaelis-Menten constant (concentration unit)
- k_{12} = distribution rate constant from compartment 1 to compartment 2
- k_{21} = distribution rate constant from compartment 2 to compartment 1
- Q = inter-compartmental clearance
- V_2 = volume of distribution of second compartment
- k_a = absorption rate constant
- $Tlag$ = lag time
- Tk_0 = absorption duration for zero order absorption
- α = first rate constant
- β = second rate constant

- A = first macro-constant
- B = second macro-constant

NB: V_1, V_2, Cl and Q are apparent volumes and clearances for extra-vascular administration.

Parameterisation

There are three parameterisations for two compartment models: (V, k, k_{12} and k_{21}), (Cl, V_1, Q and V_2) or (α, β, A and B) except for Michaelis-Menten elimination where the last parameterisation is not used. The second parameterisation terms are derived using:

- $V_1 = V$
- $Cl = k \times V_1$
- $Q = k_{12} \times V_1$
- $V_2 = \dfrac{k_{12}}{k_{21}} \times V_1$
- $\dfrac{V_1}{V_2} = \dfrac{k_{21}}{k_{12}}$

The equations are given for the third parameterisation with:

- $\alpha = \dfrac{k_{21}k}{\beta} = \dfrac{\dfrac{Q}{V_2}\dfrac{Cl}{V_1}}{\beta}$
- $\beta = \begin{cases} \dfrac{1}{2}\left[k_{12} + k_{21} + k - \sqrt{(k_{12} + k_{21} + k)^2 - 4k_{21}k}\right] \\ \dfrac{1}{2}\left[\dfrac{Q}{V_1} + \dfrac{Q}{V_2} + \dfrac{Cl}{V_1} - \sqrt{\left(\dfrac{Q}{V_1} + \dfrac{Q}{V_2} + \dfrac{Cl}{V_1}\right)^2 - 4\dfrac{Q}{V_2}\dfrac{Cl}{V_1}}\right] \end{cases}$

The link between A and B and the parameters of the first and second parameterisations depends on the input and are given in each subsection.

In the following, $C(t) = C_1$ represent the drug concentration in the first compartment and C_2 represents the drug concentration in the second compartment

1.2.1 IV bolus

- $A = \dfrac{1}{V}\dfrac{\alpha - k_{21}}{\alpha - \beta} = \dfrac{1}{V_1}\dfrac{\alpha - \dfrac{Q}{V_2}}{\alpha - \beta}$

- $B = \frac{1}{V}\frac{\beta - k_{21}}{\beta - \alpha} = \frac{1}{V_1}\frac{\beta - \frac{Q}{V_2}}{\beta - \alpha}$
- $A^e = \frac{k_{e0}A}{k_{e0} - \alpha}$
- $B^e = \frac{k_{e0}B}{k_{e0} - \beta}$

1.2.1.1 Linear elimination

- single dose

$$C(t) = D\left(Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)}\right) \tag{1.31}$$
$$C_e(t) = D\left(A^e e^{-\alpha(t-t_D)} + B^e e^{-\beta(t-t_D)} - (A^e + B^e)e^{-k_{e0}(t-t_D)}\right)$$

- multiple doses

$$C(t) = \sum_{i=1}^{n} D_i\left(Ae^{-\alpha\left(t-t_{D_i}\right)} + Be^{-\beta\left(t-t_{D_i}\right)}\right) \tag{1.32}$$
$$C_e(t) = \sum_{i=1}^{n} D_i\left(A^e e^{-\alpha\left(t-t_{D_i}\right)} + B^e e^{-\beta\left(t-t_{D_i}\right)} - (A^e + B^e)e^{-k_{e0}\left(t-t_{D_i}\right)}\right)$$

- steady state

$$C(t) = D\left(\frac{Ae^{-\alpha t}}{1 - e^{-\alpha\tau}} + \frac{Be^{-\beta t}}{1 - e^{-\beta\tau}}\right) \tag{1.33}$$
$$C_e(t) = D\left(\frac{A^e e^{-\alpha(t-t_D)}}{1 - e^{-\alpha\tau}} + \frac{B^e e^{-\beta(t-t_D)}}{1 - e^{-\beta\tau}} - \frac{(A^e + B^e)e^{-k_{e0}(t-t_D)}}{1 - e^{-k_{e0}\tau}}\right)$$

Equations 1.31 to 1.33 correspond to models n°19: bolus_2cpt_Vkk12k21, n°20: bolus_2cpt_ClV1QV2 and n°21: bolus_2cpt_alphabetaAB.

1.2.1.2 Michaelis Menten elimination

- single dose

$$\text{Initial conditions:} \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_e(t) = & 0 \text{ for } t \leq t_D \\ C_1(t_D) = & \frac{D}{V} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}\left(C_1 - C_e\right) \end{aligned} \tag{1.34}$$

- multiple doses

$C_1^{(n)}(t)$ is the concentration in the first compartment after the n^{th} dose.

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \le t_{D_1} \\ C_e(t) = & 0 \text{ for } t \le t_{D_1} \end{cases}$$

$$C_1(t_{D_1}) = C_1^{(1)}(t_{D_1}) = \frac{D_1}{V}$$

$$C_1(t_{D_n}) = C_1^{(n)}(t_{D_n}) = C_1^{(n-1)}(t_{D_n}) + \frac{D_n}{V} \tag{1.35}$$

$$\text{and when } t \neq t_{D_i}\text{: } \begin{cases} \frac{dC_1}{dt} = & -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 \\ \frac{dC_2}{dt} = & k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} = & k_{e0}(C_1 - C_e) \end{cases}$$

Equations 1.34 and 1.35 correspond to models n°22: bolus_2cpt_Vk12k21VmKm and n°23: bolus_2cpt_V1QV2VmKm.

1.2.2 IV infusion

- $A = \frac{1}{V}\frac{\alpha - k_{21}}{\alpha - \beta} = \frac{1}{V_1}\frac{\alpha - \frac{Q}{V_2}}{\alpha - \beta}$
- $B = \frac{1}{V}\frac{\beta - k_{21}}{\beta - \alpha} = \frac{1}{V_1}\frac{\beta - \frac{Q}{V_2}}{\beta - \alpha}$
- $A^e = \frac{k_{e0}A}{k_{e0} - \alpha}$
- $B^e = \frac{k_{e0}B}{k_{e0} - \beta}$

1.2.2.1 linear elimination

- single dose

$$C(t) = \begin{cases} \dfrac{D}{Tinf}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1-e^{-\alpha(t-t_D)}\right) \\ +\dfrac{B}{\beta}\left(1-e^{-\beta(t-t_D)}\right) \end{array}\right] & \text{if } t-t_D \leq Tinf, \\ \dfrac{D}{Tinf}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.36}$$

$$C_e(t) = \begin{cases} \dfrac{D}{Tinf}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha(t-t_D)}\right) \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta(t-t_D)}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}(t-t_D)}\right) \end{array}\right] & \text{if } t-t_D \leq Tinf, \\ \dfrac{D}{Tinf}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)} \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)} \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}Tinf}\right)e^{-k_{e0}(t-t_D-Tinf)} \end{array}\right] & \text{if not.} \end{cases}$$

- multiple doses

$$C(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1}\frac{D_i}{Tinf_i}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \end{array}\right] & \\ \quad +\dfrac{D}{Tinf_n}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\dfrac{B}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \end{array}\right] & \text{if } t-t_{D_n} \leq Tinf, \\ \displaystyle\sum_{i=1}^{n}\frac{D_i}{Tinf_i}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.37}$$

$$C_e(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{Tinf_i} \left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{k_{e0} Tinf_i}\right)e^{-k_{e0}\left(t-t_{D_i}-Tinf_i\right)} \end{array} \right] \\ \quad + \dfrac{D}{Tinf_n} \left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}(t-t_{D_n})}\right) \end{array} \right] & \text{if } t-t_{D_n} \leq Tinf, \\ \displaystyle\sum_{i=1}^{n} \frac{D_i}{Tinf_i} \left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0} Tinf_i}\right)e^{-k_{e0}\left(t-t_{D_i}-Tinf_i\right)} \end{array} \right] & \text{if not.} \end{cases}$$

- steady state

$$C(t) = \begin{cases} \dfrac{D}{Tinf} \left[\begin{array}{l} \dfrac{A}{\alpha}\left(\begin{array}{l} \left(1-e^{-\alpha(t-t_D)}\right) \\ +e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}} \end{array} \right) \\ +\dfrac{B}{\beta}\left(\begin{array}{l} \left(1-e^{-\beta(t-t_D)}\right) \\ +e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}} \end{array} \right) \end{array} \right] & \text{if } t-t_D \leq Tinf, \\ \dfrac{D}{Tinf} \left[\begin{array}{l} \dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}} \right) \\ +\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}} \right) \end{array} \right] & \text{if not.} \end{cases} \tag{1.38}$$

$$C_e(t)=\begin{cases}\frac{D}{Tinf}\left[\begin{array}{l}\frac{A^e}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D)}\right)\\+e^{-\alpha\tau}\frac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}}\end{array}\right)\\+\frac{B^e}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D)}\right)\\+e^{-\beta\tau}\frac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}}\end{array}\right)\\-\frac{A^e+B^e}{k_{e0}}\left(\begin{array}{l}\left(1-e^{-k_{e0}(t-t_D)}\right)\\+e^{-k_{e0}\tau}\frac{\left(1-e^{-k_{e0}Tinf}\right)e^{-k_{e0}(t-t_D-Tinf)}}{1-e^{-k_{e0}\tau}}\end{array}\right)\end{array}\right] & \text{if } t-t_D\leq Tinf,\\ \frac{D}{Tinf}\left[\begin{array}{l}\frac{A^e}{\alpha}\left(\frac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}}\right)\\+\frac{B^e}{\beta}\left(\frac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}}\right)\\-\frac{A^e+B^e}{k_{e0}}\left(\frac{\left(1-e^{-k_{e0}Tinf}\right)e^{-k_{e0}(t-t_D-Tinf)}}{1-e^{-k_{e0}\tau}}\right)\end{array}\right] & \text{if not.}\end{cases}$$

Equations 1.36 to 1.38 correspond to models n°24: infusion_2cpt_Vkk12k21, n°25: infusion_2cpt_ClV1QV2 and n°26: infusion_2cpt_alphabetaAB.

1.2.2.2 Michaelis Menten elimination

- single dose

$$\text{Initial conditions: }\begin{cases}C_1(t)= & 0 \text{ for } t<t_D\\ C_2(t)= & 0 \text{ for } t\leq t_D\\ C_e(t)= & 0 \text{ for } t\leq t_D\end{cases}$$

$$\begin{aligned}\frac{dC_1}{dt}&=-\frac{\frac{V_m}{V}\times C_1}{K_m+C_1}-k_{12}C_1+k_{12}C_2+input\\ \frac{dC_2}{dt}&=k_{21}C_1-k_{21}C_2\\ \frac{dC_e}{dt}&=k_{e0}\left(C_1-C_e\right)\\ input(t)&=\begin{cases}\frac{D}{Tinf}\frac{1}{V} & \text{if } 0\leq t-t_D\leq Tinf\\ 0 & \text{if not.}\end{cases}\end{aligned}\tag{1.39}$$

- multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \le t_{D_1} \\ C_e(t) = & 0 \text{ for } t \le t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}(C_1 - C_e) \\ input(t) &= \begin{cases} \frac{D_i}{Tinf_i}\frac{1}{V} & \text{if } 0 \le t - t_{D_i} \le Tinf_i, \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.40}$$

Equations 1.39 and 1.40 correspond to models n°27: infusion_2cpt_Vk12k21VmKm and n°28: infusion_2cpt_V1QV2VmKm.

1.2.3 First order absorption

- $A = \frac{k_a}{V}\frac{k_{21} - \alpha}{(k_a - \alpha)(\beta - \alpha)} = \frac{k_a}{V_1}\frac{\frac{Q}{V_2} - \alpha}{(k_a - \alpha)(\beta - \alpha)}$
- $B = \frac{k_a}{V}\frac{k_{21} - \beta}{(k_a - \beta)(\alpha - \beta)} = \frac{k_a}{V_1}\frac{\frac{Q}{V_2} - \beta}{(k_a - \beta)(\alpha - \beta)}$
- $A^e = \frac{k_{e0}A}{k_{e0} - \alpha}$
- $B^e = \frac{k_{e0}B}{k_{e0} - \beta}$
- $C^e = -\frac{A^e(k_a - \alpha) + B^e(k_a - \beta)}{k_a - k_{e0}}$

1.2.3.1 Linear elimination

- in absence of a lag time
  - single dose

$$C\left(t\right)=D\left(Ae^{-\alpha(t-t_D)}+Be^{-\beta(t-t_D)}-(A+B)e^{-k_a(t-t_D)}\right) \tag{1.41}$$

$$C_e\left(t\right)=D\left(A^e e^{-\alpha(t-t_D)}+B^e e^{-\beta(t-t_D)}+C^e e^{-k_{e0}(t-t_D)}-(A^e+B^e+C^e)e^{-k_a(t-t_D)}\right)$$

  - multiple doses

$$C\left(t\right)=\sum_{i=1}^{n}D_i\left(Ae^{-\alpha\left(t-t_{D_i}\right)}+Be^{-\beta\left(t-t_{D_i}\right)}-(A+B)e^{-k_a\left(t-t_{D_i}\right)}\right) \tag{1.42}$$

$$C_e\left(t\right)=\sum_{i=1}^{n}D_i\left(A^e e^{-\alpha\left(t-t_{D_i}\right)}+B^e e^{-\beta\left(t-t_{D_i}\right)}+C^e e^{-k_{e0}\left(t-t_{D_i}\right)}-(A^e+B^e+C^e)e^{-k_a\left(t-t_{D_i}\right)}\right)$$

  - steady state

$$C\left(t\right)=D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}}+\frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}}-\frac{(A+B)e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \tag{1.43}$$

$$C_e\left(t\right)=D\left(\frac{A^e e^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}}+\frac{B^e e^{-\beta(t-t_D)}}{1-e^{-\beta\tau}}+\frac{C^e e^{-k_{e0}(t-t_D)}}{1-e^{-\beta\tau}}-\frac{(A^e+B^e+C^e)e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right)$$

Equations 1.41 to 1.43 correspond to models n°29: oral1_2cpt_kaVkk12k21, n°30: oral1_2cpt_kaClV1QV2 and n°31: oral1_2cpt_kaalphabetaAB.

- in presence of a lag time
  - single dose

$$C\left(t\right)=\begin{cases}0 & \text{if } t-t_D\le Tlag,\\ D\left[\begin{array}{l}Ae^{-\alpha(t-t_D-Tlag)}+Be^{-\beta(t-t_D-Tlag)}\\ \quad -(A+B)e^{-k_a(t-t_D-Tlag)}\end{array}\right] & \text{if not.}\end{cases} \tag{1.44}$$

$$C_e\left(t\right)=\begin{cases}0 & \text{if } t-t_D\le Tlag,\\ D\left[\begin{array}{l}A^e e^{-\alpha(t-t_D-Tlag)}+B^e e^{-\beta(t-t_D-Tlag)}+C^e e^{-k_{e0}(t-t_D-Tlag)}\\ \quad -(A^e+B^e+C^e)e^{-k_a(t-t_D-Tlag)}\end{array}\right] & \text{if not.}\end{cases}$$

  - multiple doses

$$C\left(t\right)=\begin{cases}\displaystyle\sum_{i=1}^{n-1}D_i\left[\begin{array}{l}Ae^{-\alpha\left(t-t_{D_i}-Tlag\right)}+Be^{-\beta\left(t-t_{D_i}-Tlag\right)}\\ \quad -(A+B)e^{-k_a\left(t-t_{D_i}-Tlag\right)}\end{array}\right] & \text{if } t-t_{D_n}\le Tlag,\\ \displaystyle\sum_{i=1}^{n}D_i\left[\begin{array}{l}Ae^{-\alpha\left(t-t_{D_i}-Tlag\right)}+Be^{-\beta\left(t-t_{D_i}-Tlag\right)}\\ \quad -(A+B)e^{-k_a\left(t-t_{D_i}-Tlag\right)}\end{array}\right] & \text{if not.}\end{cases} \tag{1.45}$$

$$C_e(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} D_i \left[\begin{array}{r} A^e e^{-\alpha\left(t-t_{D_i}-Tlag\right)} + B^e e^{-\beta\left(t-t_{D_i}-Tlag\right)} + C^e e^{-k_{e0}\left(t-t_{D_i}-Tlag\right)} \\ -(A^e+B^e+C^e)e^{-k_a\left(t-t_{D_i}-Tlag\right)} \end{array} \right] & \text{if } t-t_{D_n} \leq Tlag, \\ \displaystyle\sum_{i=1}^{n} D_i \left[\begin{array}{r} A^e e^{-\alpha\left(t-t_{D_i}-Tlag\right)} + B^e e^{-\beta\left(t-t_{D_i}-Tlag\right)} + C^e e^{-k_{e0}\left(t-t_{D_i}-Tlag\right)} \\ -(A^e+B^e+C^e)e^{-k_a\left(t-t_{D_i}-Tlag\right)} \end{array} \right] & \text{if not.} \end{cases}$$

– steady state

$$C(t) = \begin{cases} D \left[\begin{array}{r} \dfrac{Ae^{-\alpha(t-t_D+\tau-Tlag)}}{1-e^{-\alpha\tau}} + \dfrac{Be^{-\beta(t-t_D+\tau-Tlag)}}{1-e^{-\beta\tau}} \\ -\dfrac{(A+B)e^{-k_a(t-t_D+\tau-Tlag)}}{1-e^{-k_a\tau}} \end{array} \right] & \text{if } t-t_D < Tlag, \\ D \left[\begin{array}{r} \dfrac{Ae^{-\alpha(t-t_D-Tlag)}}{1-e^{-\alpha\tau}} + \dfrac{Be^{-\beta(t-t_D-Tlag)}}{1-e^{-\beta\tau}} \\ -\dfrac{(A+B)e^{-k_a(t-t_D-Tlag)}}{1-e^{-k_a\tau}} \end{array} \right] & \text{if not.} \end{cases} \tag{1.46}$$

$$C_e(t) = \begin{cases} D \left[\begin{array}{r} \dfrac{A^e e^{-\alpha(t-t_D+\tau-Tlag)}}{1-e^{-\alpha\tau}} + \dfrac{B^e e^{-\beta(t-t_D+\tau-Tlag)}}{1-e^{-\beta\tau}} \\ +\dfrac{C^e e^{-k_{e0}(t-t_D+\tau-Tlag)}}{1-e^{-k_{e0}\tau}} \\ -\dfrac{(A^e+B^e+C^e)e^{-k_a(t-t_D+\tau-Tlag)}}{1-e^{-k_a\tau}} \end{array} \right] & \text{if } t-t_D < Tlag, \\ D \left[\begin{array}{r} \dfrac{A^e e^{-\alpha(t-t_D-Tlag)}}{1-e^{-\alpha\tau}} + \dfrac{B^e e^{-\beta(t-t_D-Tlag)}}{1-e^{-\beta\tau}} \\ +\dfrac{C^e e^{-k_{e0}(t-t_D-Tlag)}}{1-e^{-k_{e0}\tau}} \\ -\dfrac{(A^e+B^e+C^e)e^{-k_a(t-t_D-Tlag)}}{1-e^{-k_a\tau}} \end{array} \right] & \text{if not.} \end{cases}$$

Equations 1.44 to 1.46 correspond to models n°34: oral1_2cpt_TlagkaVkk12k21, n°35: oral1_2cpt_TlagkaClV1QV2 and n°36: oral1_2cpt_TlagkaalphabetaAB.

1.2.3.2 Michaelis Menten elimination

- in absence of a lag time
  - single dose

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_e(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}(C_1 - C_e) \\ input(t) &= \frac{D}{V} k_a e^{-k_a(t-t_D)} \end{aligned} \tag{1.47}$$

  - multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_e(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}(C_1 - C_e) \\ input(t) &= \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a\left(t-t_{D_i}\right)} \end{aligned} \tag{1.48}$$

Equations 1.47 and 1.48 correspond to models n°32: oral1_2cpt_kaVk12k21VmKm and n°33: oral1_2cpt_kaV1QV2VmKm.

- in presence of a lag time
  - single dose

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_e(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}(C_1 - C_e) \\ input(t) &= \begin{cases} 0 & \text{if } t - t_D < Tlag, \\ \frac{D}{V}k_a e^{-k_a(t-t_D-Tlag)} & \text{if not.} \end{cases} \end{aligned} \tag{1.49}$$

  - multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_e(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}(C_1 - C_e) \\ input(t) &= \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{V}k_a e^{-k_a\left(t-t_{D_i}-Tlag\right)} & \text{if } t - t_{D_n} < Tlag, \\ \sum_{i=1}^{n} \frac{D_i}{V}k_a e^{-k_a\left(t-t_{D_i}-Tlag\right)} & \text{if not.} \end{cases} \end{aligned} \tag{1.50}$$

Equations 1.49 and 1.50 correspond to models n°37: oral1_2cpt_TlagkaVk12k21VmKm and n°38: oral1_2cpt_TlagkaV1QV2VmKm.

1.2.4 Zero order absorption

- $A = \frac{1}{V}\frac{\alpha - k_{21}}{\alpha - \beta} = \frac{1}{V_1}\frac{\alpha - \frac{Q}{V_2}}{\alpha - \beta}$

- $B = \frac{1}{V}\frac{\beta - k_{21}}{\beta - \alpha} = \frac{1}{V_1}\frac{\beta - \frac{Q}{V_2}}{\beta - \alpha}$
- $A^e = \frac{k_{e0}A}{k_{e0} - \alpha}$
- $B^e = \frac{k_{e0}B}{k_{e0} - \beta}$

1.2.4.1 Linear elimination

- in absence of a lagtime
  - single dose

$$C(t) = \begin{cases} \frac{D}{Tk_0}\left[\begin{array}{l} \frac{A}{\alpha}\left(1 - e^{-\alpha(t-t_D)}\right) \\ +\frac{B}{\beta}\left(1 - e^{-\beta(t-t_D)}\right) \end{array}\right] & \text{if } t - t_D \leq Tk_0, \\ \frac{D}{Tk_0}\left[\begin{array}{l} \frac{A}{\alpha}\left(1 - e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)} \\ +\frac{B}{\beta}\left(1 - e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.51}$$

$$C_e(t) = \begin{cases} \frac{D}{Tk_0}\left[\begin{array}{l} \frac{A^e}{\alpha}\left(1 - e^{-\alpha(t-t_D)}\right) \\ +\frac{B^e}{\beta}\left(1 - e^{-\beta(t-t_D)}\right) \\ -\frac{A^e + B^e}{k_{e0}}\left(1 - e^{-k_{e0}(t-t_D)}\right) \end{array}\right] & \text{if } t - t_D \leq Tk_0, \\ \frac{D}{Tk_0}\left[\begin{array}{l} \frac{A^e}{\alpha}\left(1 - e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)} \\ +\frac{B^e}{\beta}\left(1 - e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)} \\ -\frac{A^e + B^e}{k_{e0}}\left(1 - e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tk_0)} \end{array}\right] & \text{if not.} \end{cases}$$

– multiple doses

$$C(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{Tk_0} \begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right) e^{-\alpha\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tk_0}\right) e^{-\beta\left(t-t_{D_i}-Tk_0\right)} \end{bmatrix} \\ \quad + \dfrac{D_n}{Tk_0} \begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\dfrac{B}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \end{bmatrix} & \text{if } t-t_{D_n} \le Tk_0, \\ \displaystyle\sum_{i=1}^{n} \frac{D_i}{Tk_0} \begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right) e^{-\alpha\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tk_0}\right) e^{-\beta\left(t-t_{D_i}-Tk_0\right)} \end{bmatrix} & \text{if not.} \end{cases} \tag{1.52}$$

$$C_e(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{Tk_0} \begin{bmatrix} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tk_0}\right) e^{-\alpha\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta Tk_0}\right) e^{-\beta\left(t-t_{D_i}-Tk_0\right)} \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0} Tk_0}\right) e^{-k_{e0}\left(t-t_{D_i}-Tk_0\right)} \end{bmatrix} \\ \quad + \dfrac{D_n}{Tk_0} \begin{bmatrix} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}(t-t_{D_n})}\right) \end{bmatrix} & \text{if } t-t_{D_n} \le Tk_0, \\ \displaystyle\sum_{i=1}^{n} \frac{D_i}{Tk_0} \begin{bmatrix} \dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tk_0}\right) e^{-\alpha\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{B^e}{\beta}\left(1-e^{-\beta Tk_0}\right) e^{-\beta\left(t-t_{D_i}-Tk_0\right)} \\ -\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0} Tk_0}\right) e^{-k_{e0}\left(t-t_{D_i}-Tk_0\right)} \end{bmatrix} & \text{if not.} \end{cases}$$

– steady state

$$C(t) = \begin{cases} \dfrac{D}{Tk_0} \begin{bmatrix} \dfrac{A}{\alpha}\left(\begin{array}{c} \left(1-e^{-\alpha(t-t_D)}\right) \\ +e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)}}{1-e^{-\alpha\tau}} \end{array} \right) \\ +\dfrac{B}{\beta}\left(\begin{array}{c} \left(1-e^{-\beta(t-t_D)}\right) \\ +e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)}}{1-e^{-\beta\tau}} \end{array} \right) \end{bmatrix} & \text{if } t-t_D \le Tk_0, \\ \dfrac{D}{Tk_0} \begin{bmatrix} \dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)}}{1-e^{-\alpha\tau}} \right) \\ +\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)}}{1-e^{-\beta\tau}} \right) \end{bmatrix} & \text{if not.} \end{cases} \tag{1.53}$$

$$C_e(t) = \begin{cases} \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D)}\right) \\ +e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)}}{1-e^{-\alpha\tau}}\end{array}\right) \\ +\dfrac{B^e}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D)}\right) \\ +e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)}}{1-e^{-\beta\tau}}\end{array}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(\begin{array}{l}\left(1-e^{-k_{e0}(t-t_D)}\right) \\ +e^{-k_{e0}\tau}\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tk_0)}}{1-e^{-k_{e0}\tau}}\end{array}\right)\end{array}\right] & \text{if } t-t_D \leq Tk_0, \\ \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)}}{1-e^{-\alpha\tau}}\right) \\ +\dfrac{B^e}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)}}{1-e^{-\beta\tau}}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tk_0)}}{1-e^{-k_{e0}\tau}}\right)\end{array}\right] & \text{if not.}\end{cases}$$

Equations 1.51 to 1.53 correspond to models n°39: oral0_2cpt_Tk0Vkk12k21, n°40: oral0_2cpt_Tk0ClV1QV2 and n°41: oral0_2cpt_Tk0alphabetaAB.

- in presence of a lag time
  - single dose

$$C(t) = \begin{cases} 0 & \text{if } t-t_D \leq Tlag, \\ \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1-e^{-\alpha(t-t_D-Tlag)}\right) \\ +\dfrac{B}{\beta}\left(1-e^{-\beta(t-t_D-Tlag)}\right)\end{array}\right] & \begin{array}{l}\text{if } Tlag < t-t_D \\ \qquad \leq Tlag+Tk_0,\end{array} \\ \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}\end{array}\right] & \text{if not.}\end{cases} \tag{1.54}$$

$$C_e(t) = \begin{cases} 0 & \text{if } t - t_D \leq Tlag, \\ \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(1 - e^{-\alpha(t-t_D-Tlag)}\right) \\ + \dfrac{B^e}{\beta}\left(1 - e^{-\beta(t-t_D-Tlag)}\right) \\ - \dfrac{A^e + B^e}{k_{e0}}\left(1 - e^{-k_{e0}(t-t_D-Tlag)}\right) \end{array}\right] & \begin{array}{l}\text{if } Tlag < t - t_D \\ \qquad \leq Tlag + Tk_0,\end{array} \\ \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(1 - e^{-\alpha Tk_0}\right) e^{-\alpha(t-t_D-Tlag-Tk_0)} \\ + \dfrac{B^e}{\beta}\left(1 - e^{-\beta Tk_0}\right) e^{-\beta(t-t_D-Tlag-Tk_0)} \\ - \dfrac{A^e + B^e}{k_{e0}}\left(1 - e^{-k_{e0} Tk_0}\right) e^{-k_{e0}(t-t_D-Tlag-Tk_0)} \end{array}\right] & \text{if not.} \end{cases}$$

– multiple doses

$$C(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{Tk_0}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1 - e^{-\alpha Tk_0}\right) e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)} \\ + \dfrac{B}{\beta}\left(1 - e^{-\beta Tk_0}\right) e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)} \end{array}\right] & \text{if } t - t_{D_n} \leq Tlag, \\ \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{Tk_0}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1 - e^{-\alpha Tk_0}\right) e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)} \\ + \dfrac{B}{\beta}\left(1 - e^{-\beta Tk_0}\right) e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)} \end{array}\right] \\ \qquad + \dfrac{D_n}{Tk_0}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1 - e^{-\alpha(t-t_{D_n}-Tlag)}\right) \\ + \dfrac{B}{\beta}\left(1 - e^{-\beta(t-t_{D_n}-Tlag)}\right) \end{array}\right] & \begin{array}{l}\text{if } Tlag < t - t_{D_n} \\ \qquad \leq Tlag + Tk_0,\end{array} \\ \displaystyle\sum_{i=1}^{n} \frac{D_i}{Tk_0}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(1 - e^{-\alpha Tk_0}\right) e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)} \\ + \dfrac{B}{\beta}\left(1 - e^{-\beta Tk_0}\right) e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.55}$$

$$C_e\left(t\right)=\begin{cases}\displaystyle\sum_{i=1}^{n-1}\frac{D_i}{Tk_0}\left[\begin{array}{l}\dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\dfrac{B^e}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)}\\-\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}\left(t-t_{D_i}-Tlag-Tk_0\right)}\end{array}\right] & \text{if } t-t_{D_n}\leq Tlag,\\ \displaystyle\sum_{i=1}^{n-1}\frac{D_i}{Tk_0}\left[\begin{array}{l}\dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\dfrac{B^e}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)}\\-\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}\left(t-t_{D_i}-Tlag-Tk_0\right)}\end{array}\right] & \text{if } Tlag<t-t_{D_n}\\ \quad+\dfrac{D_n}{Tk_0}\left[\begin{array}{l}\dfrac{A^e}{\alpha}\left(1-e^{-\alpha\left(t-t_{D_n}-Tlag\right)}\right)\\+\dfrac{B^e}{\beta}\left(1-e^{-\beta\left(t-t_{D_n}-Tlag\right)}\right)\\-\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}\left(t-t_{D_n}-Tlag\right)}\right)\end{array}\right] & \quad\leq Tlag+Tk_0,\\ \displaystyle\sum_{i=1}^{n}\frac{D_i}{Tk_0}\left[\begin{array}{l}\dfrac{A^e}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\dfrac{B^e}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)}\\-\dfrac{A^e+B^e}{k_{e0}}\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}\left(t-t_{D_i}-Tlag-Tk_0\right)}\end{array}\right] & \text{if not.}\end{cases}$$

– steady state

$$C\left(t\right)=\begin{cases}\dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\right)\\+\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\right)\end{array}\right] & \text{if } t-t_D\leq Tlag,\\ \dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D-Tlag)}\right)\\+e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\end{array}\right)\\+\dfrac{B}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D-Tlag)}\right)\\+e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\end{array}\right)\end{array}\right] & \begin{array}{l}\text{if } Tlag<t-t_D\\ \quad\leq Tlag+Tk_0,\end{array}\\ \dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\right)\\+\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\right)\end{array}\right] & \text{if not.}\end{cases}\tag{1.56}$$

$$C_e(t) = \begin{cases} \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\right) \\ +\dfrac{B^e}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-k_{e0}\tau}}\right) \end{array}\right] & \text{if } t-t_D \leq Tlag, \\ \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D-Tlag)}\right) \\ +e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\end{array}\right) \\ +\dfrac{B^e}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D-Tlag)}\right) \\ +e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\end{array}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(\begin{array}{l}\left(1-e^{-k_{e0}(t-t_D-Tlag)}\right) \\ +e^{-k_{e0}\tau}\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tlag-Tk_0)}}{1-e^{-k_{e0}\tau}}\end{array}\right) \end{array}\right] & \begin{array}{l}\text{if } Tlag < t-t_D \\ \quad \leq Tlag+Tk_0,\end{array} \\ \dfrac{D}{Tk_0}\left[\begin{array}{l} \dfrac{A^e}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\right) \\ +\dfrac{B^e}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\right) \\ -\dfrac{A^e+B^e}{k_{e0}}\left(\dfrac{\left(1-e^{-k_{e0}Tk_0}\right)e^{-k_{e0}(t-t_D-Tlag-Tk_0)}}{1-e^{-k_{e0}\tau}}\right) \end{array}\right] & \text{if not.} \end{cases}$$

Equations 1.54 to 1.56 correspond to models n°44: oral0_2cpt_TlagTk0Vkk12k21, n°45: oral0_2cpt_TlagTk0ClV1QV2 and n°46: oral0_2cpt_TlagTk0alphabetaAB.

1.2.4.2 Michaelis Menten elimination

- in absence of a lagtime
  - single dose

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_e(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}(C_1 - C_e) \\ input(t) &= \begin{cases} \frac{D}{Tk_0}\frac{1}{V} & \text{if } 0 \leq t - t_D \leq Tk_0 \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.57}$$

  - multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_e(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}(C_1 - C_e) \\ input(t) &= \begin{cases} \frac{D_i}{Tk_0}\frac{1}{V} & \text{if } 0 \leq t - t_{D_i} \leq Tk_0, \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.58}$$

Equations 1.57 and 1.58 correspond to models n°42: oral0_2cpt_Tk0Vk12k21VmKm and n°43: oral0_2cpt_Tk0V1QV2VmKm.

- in presence of a lag time
  - single dose

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_e(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}\left(C_1 - C_e\right) \end{aligned} \tag{1.59}$$

$$input(t) = \begin{cases} 0 & \text{if } 0 \leq t - t_D \leq Tlag, \\ \frac{D}{Tk_0}\frac{1}{V} & \text{if } Tlag < t - t_D \leq Tlag + Tk_0, \\ 0 & \text{if not.} \end{cases}$$

  - multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_e(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_e}{dt} &= k_{e0}\left(C_1 - C_e\right) \end{aligned} \tag{1.60}$$

$$input(t) = \begin{cases} 0 & \text{if } 0 \leq t - t_{D_i} \leq Tlag, \\ \frac{D_i}{Tk_0}\frac{1}{V} & \text{if } Tlag < t - t_{D_i} \leq Tlag + Tk_0, \\ 0 & \text{if not.} \end{cases}$$

Equations 1.59 and 1.60 correspond to models n°47: oral0_2cpt_TlagTk0Vk12k21VmKm and n°48: oral0_2cpt_TlagTk0V1QV2VmKm.

1.3 Three compartment models

The three compartment model implemented in Monolix is described in figure 1.2.

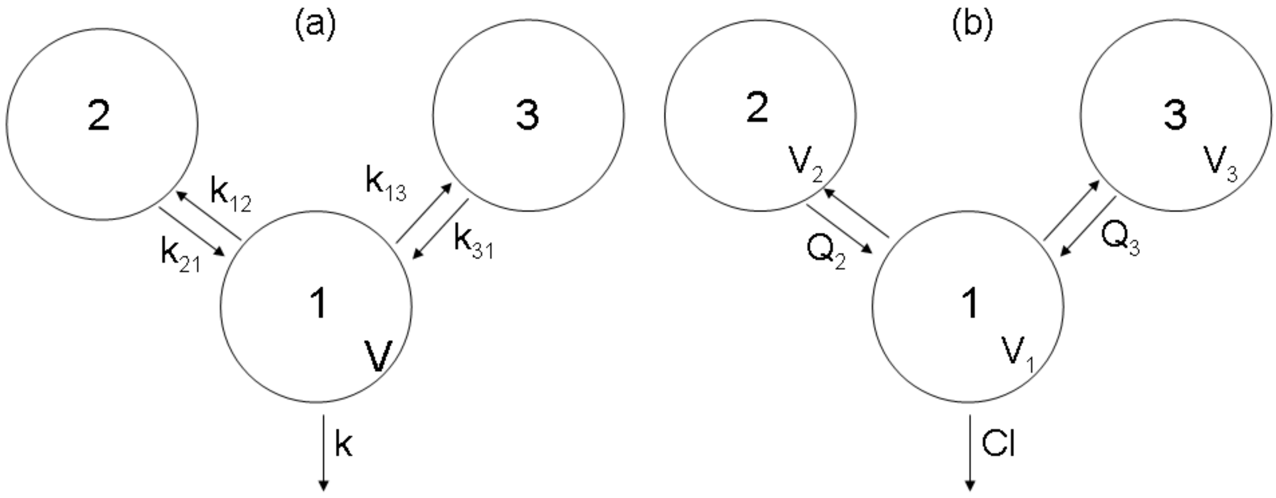

Figure 1.2: The mammillary model with three compartments implemented in Monolix, parameterized in micro-constants V, k, k_{12}, k_{21}, k_{13} and k_{31} (a) or with Cl, V_1, Q_2, V_2 Q_3 and V_3 (b)

Parameters

- $V = V_1$ = volume of distribution of first compartment
- k = elimination rate constant
- Cl = clearance of elimination
- V_m = maximum elimination rate (amount per time unit)
- K_m = Michaelis-Menten constant (concentration unit)
- k_{12} = distribution rate constant from compartment 1 to compartment 2
- k_{21} = distribution rate constant from compartment 2 to compartment 1
- Q_2 = inter-compartmental clearance from compartment 1 to compartment 2
- V_2 = volume of distribution of second compartment
- k_{13} = distribution rate constant from compartment 1 to compartment 3
- k_{31} = distribution rate constant from compartment 3 to compartment 1
- Q_3 = inter-compartmental clearance from compartment 1 to compartment 3

- V_3 = volume of distribution of third compartment
- k_a = absorption rate constant
- $Tlag$ = lag time
- Tk_0 = absorption duration for zero order absorption
- α = first rate constant
- β = second rate constant
- γ = third rate constant
- A = first macro-constant
- B = second macro-constant
- C = third macro-constant

NB: V_1, V_2, V_3, Cl, Q_2 and Q_3 are apparent volumes and clearances for extra-vascular administration.

Parameterisation

There are three parameterisations for three compartment models: (V, k, k_{12}, k_{21}, k_{13} and k_{31}), (Cl, V_1, Q_2, V_2, Q_3 and V_3) or (α, β, γ, A, B and C) except for Michaelis-Menten elimination where the last parameterisation is not used. The second parameterisation terms are derived using:

- $V_1 = V$
- $Cl = k \times V_1$
- $Q_2 = k_{12} \times V_1$
- $V_2 = \frac{k_{12}}{k_{21}} \times V_1$
- $Q_3 = k_{13} \times V_1$
- $V_3 = \frac{k_{13}}{k_{31}} \times V_1$

The equations are given for the third parameterisation with:

- $a_0 = kk_{21}k_{31} = \frac{Cl}{V_1}\frac{Q_2}{V_2}\frac{Q_3}{V_3}$
- $a_1 = \begin{cases} kk_{31} + k_{21}k_{31} + k_{21}k_{13} + kk_{21} + k_{31}k_{12} \\ \frac{Cl}{V_1}\frac{Q_3}{V_3} + \frac{Q_2}{V_2}\frac{Q_3}{V_3} + \frac{Q_2}{V_2}\frac{Q_3}{V_1} + \frac{Cl}{V_1}\frac{Q_2}{V_2} + \frac{Q_3}{V_3}\frac{Q_2}{V_1} \end{cases}$
- $a_2 = \begin{cases} k + k_{12} + k_{13} + k_{21} + k_{31} \\ \frac{Cl}{V_1} + \frac{Q_2}{V_1} + \frac{Q_3}{V_1} + \frac{Q_2}{V_2} + \frac{Q_3}{V_3} \end{cases}$
- $p = a_1 - a_2^2/3$
- $q = 2a_2^3/27 - a_1a_2/3 + a_0$
- $r_1 = \sqrt{-\left(p^3/27\right)}$
- $r_2 = 2r_1^{1/3}$
- $\phi = \arccos\left(-\frac{q}{2r_1}\right)/3$
- $\alpha = -\left(\cos\left(\phi\right)r_2 - a_2/3\right)$
- $\beta = -\left(\cos\left(\phi + \frac{2\pi}{3}\right)r_2 - a_2/3\right)$
- $\gamma = -\left(\cos\left(\phi + \frac{4\pi}{3}\right)r_2 - a_2/3\right)$

The link between A, B, C and the parameters of the first and second parameterisations depends on the input and are given in each subsection.

In the following, $C\left(t\right) = C_1$ represents the drug concentration in the first compartment, C_2 represents the drug concentration in the second compartment and C_3 represents the drug concentration in the third compartment.

1.3.1 IV bolus

- $A = \frac{1}{V}\frac{k_{21}-\alpha}{\alpha-\beta}\frac{k_{31}-\alpha}{\alpha-\gamma} = \frac{1}{V_1}\frac{\frac{Q_2}{V_2}-\alpha}{\alpha-\beta}\frac{\frac{Q_3}{V_3}-\alpha}{\alpha-\gamma}$
- $B = \frac{1}{V}\frac{k_{21}-\beta}{\beta-\alpha}\frac{k_{31}-\beta}{\beta-\gamma} = \frac{1}{V_1}\frac{\frac{Q_2}{V_2}-\beta}{\beta-\alpha}\frac{\frac{Q_3}{V_3}-\beta}{\beta-\gamma}$
- $C = \frac{1}{V}\frac{k_{21}-\gamma}{\gamma-\beta}\frac{k_{31}-\gamma}{\gamma-\alpha} = \frac{1}{V_1}\frac{\frac{Q_2}{V_2}-\gamma}{\gamma-\beta}\frac{\frac{Q_3}{V_3}-\gamma}{\gamma-\alpha}$

1.3.1.1 Linear elimination

- single dose

$$C\left(t\right)=D\left(Ae^{-\alpha\left(t-t_D\right)}+Be^{-\beta\left(t-t_D\right)}+Ce^{-\gamma\left(t-t_D\right)}\right) \tag{1.61}$$

- multiple doses

$$C\left(t\right)=\sum_{i=1}^{n}D_i\left(Ae^{-\alpha\left(t-tD_i\right)}+Be^{-\beta\left(t-tD_i\right)}+Ce^{-\gamma\left(t-tD_i\right)}\right) \tag{1.62}$$

- steady state

$$C\left(t\right)=D\left(\frac{Ae^{-\alpha\left(t-t_D\right)}}{1-e^{-\alpha\tau}}+\frac{Be^{-\beta\left(t-t_D\right)}}{1-e^{-\beta\tau}}+\frac{Ce^{-\gamma\left(t-t_D\right)}}{1-e^{-\gamma\tau}}\right) \tag{1.63}$$

Equations 1.61 to 1.63 correspond to models n°49: bolus_3cpt_Vkk12k21k13k31, n°50: bolus_2cpt_ClV1Q2V2Q3V3 and n°51: bolus_3cpt_alphabetagammaABC.

1.3.1.2 Michaelis Menten elimination

- single dose

$$\text{Initial conditions:}\begin{cases}C_1\left(t\right)= & 0 \text{ for } t<t_D\\ C_2\left(t\right)= & 0 \text{ for } t\leq t_D\\ C_3\left(t\right)= & 0 \text{ for } t\leq t_D\\ C_1\left(t_D\right)= & \dfrac{D}{V}\end{cases}$$

$$\begin{aligned}\frac{dC_1}{dt}&=-\frac{\frac{V_m}{V}\times C_1}{K_m+C_1}-k_{12}C_1+k_{12}C_2-k_{13}C_1+k_{13}C_3\\ \frac{dC_2}{dt}&=k_{21}C_1-k_{21}C_2\\ \frac{dC_3}{dt}&=k_{31}C_1-k_{31}C_3\end{aligned} \tag{1.64}$$

- multiple doses

$C_1^{(n)}(t)$ is the concentration in the first compartment after the n^{th} dose.

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_3(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$C_1(t_{D_1}) = C_1^{(1)}(t_{D_1}) = \frac{D_1}{V}$$

$$C_1(t_{D_n}) = C_1^{(n)}(t_{D_n}) = C_1^{(n-1)}(t_{D_n}) + \frac{D_n}{V} \tag{1.65}$$

$$\text{and when } t \neq t_{D_i}\text{: } \begin{cases} \dfrac{dC_1}{dt} = & -\dfrac{\dfrac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 \\ \dfrac{dC_2}{dt} = & k_{21}C_1 - k_{21}C_2 \\ \dfrac{dC_3}{dt} = & k_{31}C_1 - k_{31}C_3 \end{cases}$$

Equations 1.64 and 1.65 correspond to models n°52: bolus_3cpt_Vk12k21k13k31VmKm and n°53: bolus_3cpt_V1Q2V2Q3V3VmKm.

1.3.2 IV infusion

- $A = \dfrac{1}{V} \dfrac{k_{21} - \alpha}{\alpha - \beta} \dfrac{k_{31} - \alpha}{\alpha - \gamma} = \dfrac{1}{V_1} \dfrac{\dfrac{Q_2}{V_2} - \alpha}{\alpha - \beta} \dfrac{\dfrac{Q_3}{V_3} - \alpha}{\alpha - \gamma}$

- $B = \dfrac{1}{V} \dfrac{k_{21} - \beta}{\beta - \alpha} \dfrac{k_{31} - \beta}{\beta - \gamma} = \dfrac{1}{V_1} \dfrac{\dfrac{Q_2}{V_2} - \beta}{\beta - \alpha} \dfrac{\dfrac{Q_3}{V_3} - \beta}{\beta - \gamma}$

- $C = \dfrac{1}{V} \dfrac{k_{21} - \gamma}{\gamma - \beta} \dfrac{k_{31} - \gamma}{\gamma - \alpha} = \dfrac{1}{V_1} \dfrac{\dfrac{Q_2}{V_2} - \gamma}{\gamma - \beta} \dfrac{\dfrac{Q_3}{V_3} - \gamma}{\gamma - \alpha}$

1.3.2.1 linear elimination

- single dose

$$C(t) = \begin{cases} \frac{D}{Tinf}\begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha(t-t_D)}\right) \\ +\frac{B}{\beta}\left(1-e^{-\beta(t-t_D)}\right) \\ +\frac{C}{\gamma}\left(1-e^{-\gamma(t-t_D)}\right) \end{bmatrix} & \text{if } t-t_D \leq Tinf, \\ \frac{D}{Tinf}\begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)} \\ +\frac{C}{\gamma}\left(1-e^{-\gamma Tinf}\right)e^{-\gamma(t-t_D-Tinf)} \end{bmatrix} & \text{if not.} \end{cases} \tag{1.66}$$

- multiple doses

$$C(t) = \begin{cases} \sum_{i=1}^{n-1}\frac{D_i}{Tinf_i}\begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{C}{\gamma}\left(1-e^{-\gamma Tinf_i}\right)e^{-\gamma\left(t-t_{D_i}-Tinf_i\right)} \end{bmatrix} \\ \quad +\frac{D}{Tinf_n}\begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\frac{B}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \\ +\frac{C}{\gamma}\left(1-e^{-\gamma(t-t_{D_n})}\right) \end{bmatrix} & \text{if } t-t_{D_n} \leq Tinf, \\ \sum_{i=1}^{n}\frac{D_i}{Tinf_i}\begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{C}{\gamma}\left(1-e^{-\gamma Tinf_i}\right)e^{-\gamma\left(t-t_{D_i}-Tinf_i\right)} \end{bmatrix} & \text{if not.} \end{cases} \tag{1.67}$$

- steady state

$$C(t) = \begin{cases} \dfrac{D}{Tinf}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D)}\right) \\ +\,e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}}\end{array}\right) \\ +\dfrac{B}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D)}\right) \\ +\,e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}}\end{array}\right) \\ +\dfrac{C}{\gamma}\left(\begin{array}{l}\left(1-e^{-\gamma(t-t_D)}\right) \\ +\,e^{-\gamma\tau}\dfrac{\left(1-e^{-\gamma Tinf}\right)e^{-\gamma(t-t_D-Tinf)}}{1-e^{-\gamma\tau}}\end{array}\right) \end{array}\right] & \text{if } t-t_D \leq Tinf, \\ \dfrac{D}{Tinf}\left[\begin{array}{l} \dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}}\right) \\ +\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}}\right) \\ +\dfrac{C}{\gamma}\left(\dfrac{\left(1-e^{-\gamma Tinf}\right)e^{-\gamma(t-t_D-Tinf)}}{1-e^{-\gamma\tau}}\right) \end{array}\right] & \text{if not.} \end{cases} \tag{1.68}$$

Equations 1.66 to 1.68 correspond to models n°54: infusion_3cpt_Vkk12k21k13k31, n°55: infusion_3cpt_ClV1Q2V2Q3V3 and n°56: infusion_3cpt_alphabetagammaABC.

1.3.2.2 Michaelis Menten elimination

- single dose

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_3(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} \dfrac{D}{Tinf}\dfrac{1}{V} & \text{if } 0 \leq t - t_D \leq Tinf \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.69}$$

- multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_3(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} \frac{D_i}{Tinf_i}\frac{1}{V} & \text{if } 0 \leq t - t_{D_i} \leq Tinf_i, \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.70}$$

Equations 1.69 and 1.70 correspond to models n°57: infusion_3cpt_Vk12k21k13k31VmKm and n°58: infusion_3cpt_V1Q2V2Q3V3VmKm.

1.3.3 First order absorption

- $A = \frac{1}{V}\frac{k_a}{k_a - \alpha}\frac{k_{21} - \alpha}{\alpha - \beta}\frac{k_{31} - \alpha}{\alpha - \gamma} = \frac{1}{V_1}\frac{k_a}{k_a - \alpha}\frac{\frac{Q_2}{V_2} - \alpha}{\alpha - \beta}\frac{\frac{Q_3}{V_3} - \alpha}{\alpha - \gamma}$

- $B = \frac{1}{V}\frac{k_a}{k_a - \beta}\frac{k_{21} - \beta}{\beta - \alpha}\frac{k_{31} - \beta}{\beta - \gamma} = \frac{1}{V_1}\frac{k_a}{k_a - \beta}\frac{\frac{Q_2}{V_2} - \beta}{\beta - \alpha}\frac{\frac{Q_3}{V_3} - \beta}{\beta - \gamma}$

- $C = \frac{1}{V}\frac{k_a}{k_a - \gamma}\frac{k_{21} - \gamma}{\gamma - \beta}\frac{k_{31} - \gamma}{\gamma - \alpha} = \frac{1}{V_1}\frac{k_a}{k_a - \gamma}\frac{\frac{Q_2}{V_2} - \gamma}{\gamma - \beta}\frac{\frac{Q_3}{V_3} - \gamma}{\gamma - \alpha}$

1.3.3.1 Linear elimination

- in absence of a lag time

  - single dose

$$C(t) = D\left(Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)} + Ce^{-\gamma(t-t_D)} - (A+B+C)e^{-k_a(t-t_D)}\right) \tag{1.71}$$

  - multiple doses

$$C(t) = \sum_{i=1}^{n} D_i\left(Ae^{-\alpha\left(t-t_{D_i}\right)} + Be^{-\beta\left(t-t_{D_i}\right)} + Ce^{-\gamma\left(t-t_{D_i}\right)} - (A+B+C)e^{-k_a\left(t-t_{D_i}\right)}\right) \tag{1.72}$$

– steady state

$$C(t) = D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}} + \frac{Ce^{-\gamma(t-t_D)}}{1-e^{-\gamma\tau}} - \frac{(A+B+C)e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \tag{1.73}$$

Equations 1.71 to 1.73 correspond to models n°59: oral1_3cpt_kaVkk12k21k13k31, n°60: oral1_3cpt_kaClV1Q2V2Q3V3 and n°61: oral1_3cpt_kaalphabetagammaABC.

- in presence of a lag time

  – single dose

$$C(t) = \begin{cases} 0 & \text{if } t-t_D \le Tlag, \\ D\left[\begin{array}{l} Ae^{-\alpha(t-t_D-Tlag)} + Be^{-\beta(t-t_D-Tlag)} \\ + Ce^{-\gamma(t-t_D-Tlag)} - (A+B+C)e^{-k_a(t-t_D-Tlag)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.74}$$

  – multiple doses

$$C(t) = \begin{cases} \sum_{i=1}^{n-1} D_i \left[\begin{array}{l} Ae^{-\alpha\left(t-t_{D_i}-Tlag\right)} + Be^{-\beta\left(t-t_{D_i}-Tlag\right)} \\ + Ce^{-\gamma\left(t-t_{D_i}-Tlag\right)} - (A+B+C)e^{-k_a\left(t-t_{D_i}-Tlag\right)} \end{array}\right] & \text{if } t-t_{D_n} \le Tlag, \\ \sum_{i=1}^{n} D_i \left[\begin{array}{l} Ae^{-\alpha\left(t-t_{D_i}-Tlag\right)} + Be^{-\beta\left(t-t_{D_i}-Tlag\right)} \\ + Ce^{-\gamma\left(t-t_{D_i}-Tlag\right)} - (A+B+C)e^{-k_a\left(t-t_{D_i}-Tlag\right)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.75}$$

  – steady state

$$C(t) = \begin{cases} D\left[\begin{array}{l} \frac{Ae^{-\alpha(t-t_D+\tau-Tlag)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D+\tau-Tlag)}}{1-e^{-\beta\tau}} \\ \quad + \frac{Ce^{-\gamma(t-t_D+\tau-Tlag)}}{1-e^{-\gamma\tau}} - \frac{(A+B+C)e^{-k_a(t-t_D+\tau-Tlag)}}{1-e^{-k_a\tau}} \end{array}\right] & \text{if } t-t_D < Tlag, \\ D\left[\begin{array}{l} \frac{Ae^{-\alpha(t-t_D-Tlag)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D-Tlag)}}{1-e^{-\beta\tau}} \\ \quad + \frac{Ce^{-\gamma(t-t_D-Tlag)}}{1-e^{-\gamma\tau}} - \frac{(A+B+C)e^{-k_a(t-t_D-Tlag)}}{1-e^{-k_a\tau}} \end{array}\right] & \text{if not.} \end{cases} \tag{1.76}$$

Equations 1.74 to 1.76 correspond to models n°64: oral1_3cpt_TlagkaVkk12k21k13K31, n°65: oral1_3cpt_TlagkaClV1Q2V2Q3V3 and n°66: oral1_3cpt_TlagkaalphabetagammaABC.

1.3.3.2 Michaelis Menten elimination

- in absence of a lag time
  - single dose

$$\text{Initial conditions:} \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_3(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \frac{D}{V} k_a e^{-k_a(t-t_D)} \end{aligned} \tag{1.77}$$

  - multiple doses

$$\text{Initial conditions:} \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_3(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a\left(t-t_{D_i}\right)} \end{aligned} \tag{1.78}$$

Equations 1.77 and 1.78 correspond to models n°62: oral1_3cpt_kaVk12k21k13k31VmKm and n°63: oral1_3cpt_kaV1Q2V2Q3V3VmKm.

- in presence of a lag time
  - single dose

$$\text{Initial conditions:} \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_3(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} 0 & \text{if } t - t_D < Tlag, \\ \frac{D}{V} k_a e^{-k_a(t - t_D - Tlag)} & \text{if not.} \end{cases} \end{aligned} \tag{1.79}$$

  - multiple doses

$$\text{Initial conditions:} \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_3(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{V} k_a e^{-k_a\left(t - t_{D_i} - Tlag\right)} & \text{if } t - t_{D_n} < Tlag, \\ \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a\left(t - t_{D_i} - Tlag\right)} & \text{if not.} \end{cases} \end{aligned} \tag{1.80}$$

Equations 1.79 and 1.80 correspond to models n°67: oral1_3cpt_TlagkaVk12k21k13k31VmKm and n°68: oral1_3cpt_TlagkaV1Q2V2Q3V3VmKm.

1.3.4 Zero order absorption

- $A = \frac{1}{V} \frac{k_{21} - \alpha}{\alpha - \beta} \frac{k_{31} - \alpha}{\alpha - \gamma} = \frac{1}{V_1} \frac{\frac{Q_2}{V_2} - \alpha}{\alpha - \beta} \frac{\frac{Q_3}{V_3} - \alpha}{\alpha - \gamma}$

- $B = \dfrac{1}{V}\dfrac{k_{21}-\beta}{\beta-\alpha}\dfrac{k_{31}-\beta}{\beta-\gamma} = \dfrac{1}{V_1}\dfrac{\dfrac{Q_2}{V_2}-\beta}{\beta-\alpha}\dfrac{\dfrac{Q_3}{V_3}-\beta}{\beta-\gamma}$
- $C = \dfrac{1}{V}\dfrac{k_{21}-\gamma}{\gamma-\beta}\dfrac{k_{31}-\gamma}{\gamma-\alpha} = \dfrac{1}{V_1}\dfrac{\dfrac{Q_2}{V_2}-\gamma}{\gamma-\beta}\dfrac{\dfrac{Q_3}{V_3}-\gamma}{\gamma-\alpha}$

1.3.4.1 Linear elimination

- in absence of a lagtime
  - single dose

$$C(t) = \begin{cases} \dfrac{D}{Tk_0}\begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha(t-t_D)}\right) \\ +\dfrac{B}{\beta}\left(1-e^{-\beta(t-t_D)}\right) \\ +\dfrac{C}{\gamma}\left(1-e^{-\gamma(t-t_D)}\right) \end{bmatrix} & \text{if } t-t_D \leq Tk_0, \\ \dfrac{D}{Tk_0}\begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)} \\ +\dfrac{C}{\gamma}\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma(t-t_D-Tk_0)} \end{bmatrix} & \text{if not.} \end{cases} \tag{1.81}$$

  - multiple doses

$$C(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1}\dfrac{D_i}{Tk_0}\begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{C}{\gamma}\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma\left(t-t_{D_i}-Tk_0\right)} \end{bmatrix} \\ \quad +\dfrac{D_n}{Tk_0}\begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\dfrac{B}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \\ +\dfrac{C}{\gamma}\left(1-e^{-\gamma(t-t_{D_n})}\right) \end{bmatrix} & \text{if } t-t_{D_n} \leq Tk_0, \\ \displaystyle\sum_{i=1}^{n}\dfrac{D_i}{Tk_0}\begin{bmatrix} \dfrac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tk_0\right)} \\ +\dfrac{C}{\gamma}\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma\left(t-t_{D_i}-Tk_0\right)} \end{bmatrix} & \text{if not.} \end{cases} \tag{1.82}$$

– steady state

$$C(t)=\begin{cases}\dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D)}\right)\\+e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)}}{1-e^{-\alpha\tau}}\end{array}\right)\\+\dfrac{B}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D)}\right)\\+e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)}}{1-e^{-\beta\tau}}\end{array}\right)\\+\dfrac{C}{\gamma}\left(\begin{array}{l}\left(1-e^{-\gamma(t-t_D)}\right)\\+e^{-\gamma\tau}\dfrac{\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma(t-t_D-Tk_0)}}{1-e^{-\gamma\tau}}\end{array}\right)\end{array}\right] & \text{if } t-t_D\leq Tk_0,\\ \dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tk_0)}}{1-e^{-\alpha\tau}}\right)\\+\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tk_0)}}{1-e^{-\beta\tau}}\right)\\+\dfrac{C}{\gamma}\left(\dfrac{\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma(t-t_D-Tk_0)}}{1-e^{-\gamma\tau}}\right)\end{array}\right] & \text{if not.}\end{cases} \tag{1.83}$$

Equations 1.81 to 1.83 correspond to models n°69: oral0_3cpt_Tk0Vkk12k21k13K31, n°70: oral0_3cpt_Tk0ClV1Q2V2Q3V3 and n°71: oral0_3cpt_Tk0alphabetagammaABC.

- in presence of a lag time

  – single dose

$$C(t)=\begin{cases}0 & \text{if } t-t_D\leq Tlag,\\ \dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(1-e^{-\alpha(t-t_D-Tlag)}\right)\\+\dfrac{B}{\beta}\left(1-e^{-\beta(t-t_D-Tlag)}\right)\\+\dfrac{C}{\gamma}\left(1-e^{-\gamma(t-t_D-Tlag)}\right)\end{array}\right] & \text{if } Tlag<t-t_D\leq Tlag+Tk_0,\\ \dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)}\\+\dfrac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}\\+\dfrac{C}{\gamma}\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma(t-t_D-Tlag-Tk_0)}\end{array}\right] & \text{if not.}\end{cases} \tag{1.84}$$

– multiple doses

$$C(t)=\begin{cases}\displaystyle\sum_{i=1}^{n-1}\frac{D_i}{Tk_0}\begin{bmatrix}\frac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\frac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\frac{C}{\gamma}\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma\left(t-t_{D_i}-Tlag-Tk_0\right)}\end{bmatrix} & \text{if } t-t_{D_n}\leq Tlag,\\ \begin{array}{l}\displaystyle\sum_{i=1}^{n-1}\frac{D_i}{Tk_0}\begin{bmatrix}\frac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\frac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\frac{C}{\gamma}\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma\left(t-t_{D_i}-Tlag-Tk_0\right)}\end{bmatrix}\\ \displaystyle+\frac{D_n}{Tk_0}\begin{bmatrix}\frac{A}{\alpha}\left(1-e^{-\alpha(t-t_{D_n}-Tlag)}\right)\\+\frac{B}{\beta}\left(1-e^{-\beta(t-t_{D_n}-Tlag)}\right)\\+\frac{C}{\gamma}\left(1-e^{-\gamma(t-t_{D_n}-Tlag)}\right)\end{bmatrix}\end{array} & \text{if } Tlag<t-t_{D_n}\leq Tlag+Tk_0,\\ \displaystyle\sum_{i=1}^{n}\frac{D_i}{Tk_0}\begin{bmatrix}\frac{A}{\alpha}\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\frac{B}{\beta}\left(1-e^{-\beta Tk_0}\right)e^{-\beta\left(t-t_{D_i}-Tlag-Tk_0\right)}\\+\frac{C}{\gamma}\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma\left(t-t_{D_i}-Tlag-Tk_0\right)}\end{bmatrix} & \text{if not.}\end{cases}\tag{1.85}$$

– steady state

$$C(t)=\begin{cases}\dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\right)\\+\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\right)\\+\dfrac{C}{\gamma}\left(\dfrac{\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma(t-t_D+\tau-Tlag-Tk_0)}}{1-e^{-\gamma\tau}}\right)\end{array}\right] & \text{if } t-t_D\leq Tlag,\\ \dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D-Tlag)}\right)\\+e^{-\alpha\tau}\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\end{array}\right)\\+\dfrac{B}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D-Tlag)}\right)\\+e^{-\beta\tau}\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\end{array}\right)\\+\dfrac{C}{\gamma}\left(\begin{array}{l}\left(1-e^{-\gamma(t-t_D-Tlag)}\right)\\+e^{-\gamma\tau}\dfrac{\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma(t-t_D-Tlag-Tk_0)}}{1-e^{-\gamma\tau}}\end{array}\right)\end{array}\right] & \begin{array}{l}\text{if } Tlag<t-t_D\\ \quad\leq Tlag+Tk_0,\end{array}\\ \dfrac{D}{Tk_0}\left[\begin{array}{l}\dfrac{A}{\alpha}\left(\dfrac{\left(1-e^{-\alpha Tk_0}\right)e^{-\alpha(t-t_D-Tlag-Tk_0)}}{1-e^{-\alpha\tau}}\right)\\+\dfrac{B}{\beta}\left(\dfrac{\left(1-e^{-\beta Tk_0}\right)e^{-\beta(t-t_D-Tlag-Tk_0)}}{1-e^{-\beta\tau}}\right)\\+\dfrac{C}{\gamma}\left(\dfrac{\left(1-e^{-\gamma Tk_0}\right)e^{-\gamma(t-t_D-Tlag-Tk_0)}}{1-e^{-\gamma\tau}}\right)\end{array}\right] & \text{if not.}\end{cases} \tag{1.86}$$

Equations 1.84 to 1.86 correspond to models n°74: oral0_3cpt_TlagTk0Vkk12k21k13K31, n°75: oral0_3cpt_TlagTk0ClV1Q2V2Q3V3 and n°76: oral0_3cpt_TlagTk0alphabetagammaABC.

1.3.4.2 Michaelis Menten elimination

- in absence of a lagtime
  - single dose

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_3(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} \frac{D}{Tk_0}\frac{1}{V} & \text{if } 0 \leq t - t_D \leq Tk_0 \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.87}$$

  - multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_3(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} \frac{D_i}{Tk_0}\frac{1}{V} & \text{if } 0 \leq t - t_{D_i} \leq Tk_0, \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.88}$$

Equations 1.87 and 1.88 correspond to models n°72: oral0_3cpt_Tk0Vk12k21k13k31VmKm and n°73: oral0_3cpt_Tk0V1Q2V2Q3V3VmKm.

- in presence of a lag time
  - single dose

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \\ C_3(t) = & 0 \text{ for } t \leq t_D \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} 0 & \text{if } 0 \leq t - t_D \leq Tlag, \\ \frac{D}{Tk_0}\frac{1}{V} & \text{if } Tlag < t - t_D \leq Tlag + Tk_0, \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.89}$$

  - multiple doses

$$\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \\ C_3(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases}$$

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{\frac{V_m}{V} \times C_1}{K_m + C_1} - k_{12}C_1 + k_{12}C_2 - k_{13}C_1 + k_{13}C_3 + input \\ \frac{dC_2}{dt} &= k_{21}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= k_{31}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} 0 & \text{if } 0 \leq t - t_{D_i} \leq Tlag, \\ \frac{D_i}{Tk_0}\frac{1}{V} & \text{if } Tlag < t - t_{D_i} \leq Tlag + Tk_0, \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.90}$$

Equations 1.89 and 1.90 correspond to models n°77: oral0_3cpt_TlagTk0Vk12k21k13k31VmKm and n°78: oral0_3cpt_TlagTk0V1Q2V2Q3V3VmKm.

Chapter 2

Pharmacodynamic models

This chapter describe the pharmacodynamic models implemented in the Monolix software. Some of these pharmacodynamic models can be used alone or linked to any pharmacokinetic model. Some can only be used linked to any pharmacokinetic model. Two different type of models are presented here:

- The immediate response models (alone or linked to a pharmacokinetic model)
- The turnover models (only linked to a pharmacokinetic model)

2.1 Immediate response models

For these response models, the effect $E(t)$ is expressed as:

$$E(t) = A(t) + S(t) \tag{2.1}$$

where $A(t)$ represents the model of drug action and $S(t)$ corresponds to the baseline/disease model. $A(t)$ is a function of the concentration $C(t)$ in the central compartment or of the concentration $C_e(t)$ in the effect compartment (not available for three compartments models).

The drug action models are presented in section 2.1.1 for $C(t)$. The baseline/disease models are presented in section 2.1.2. Any combination of those two models is available in the Monolix library and their name are given in section 2.1.3.

Parameters

- A_{lin} = constant associated to $C(t)$
- A_{quad} = constant associated to the square of $C(t)$
- A_{log} = constant associated to the logarithm of $C(t)$
- E_{max} = maximal agonistic response
- I_{max} = maximal antagonistic response
- C_{50} = concentration to get half of the maximal response (=drug potency)

- γ = sigmoidicity factor
- S_0 = baseline value of the studied effect
- k_{prog} = rate constant of disease progression

2.1.1 Drug action models

- linear model
$$A(t) = A_{lin}C(t) \tag{2.2}$$
- quadratic model
$$A(t) = A_{lin}C(t) + A_{quad}C(t)^2 \tag{2.3}$$
- logarithmic model
$$A(t) = A_{log}log(C(t)) \tag{2.4}$$
- E_{max} model
$$A(t) = \frac{E_{max}C(t)}{C(t) + C_{50}} \tag{2.5}$$
- sigmoïd E_{max} model
$$A(t) = \frac{E_{max}C(t)^\gamma}{C(t)^\gamma + C_{50}^\gamma} \tag{2.6}$$
- I_{max} model
$$A(t) = 1 - \frac{I_{max}C(t)}{C(t) + C_{50}} \tag{2.7}$$
- sigmoïd I_{max} model
$$A(t) = 1 - \frac{I_{max}C(t)^\gamma}{C(t)^\gamma + C_{50}^\gamma} \tag{2.8}$$

2.1.2 Baseline/disease models

- null baseline
$$S(t) = 0 \tag{2.9}$$
- constant baseline with no disease progression
$$S(t) = S_0 \tag{2.10}$$
- linear disease progression
$$S(t) = S_0 + k_{prog}t \tag{2.11}$$
- exponential disease increase
$$S(t) = S_0 e^{-k_{prog}t} \tag{2.12}$$
- exponential disease decrease
$$S(t) = S_0\left(1 - e^{-k_{prog}t}\right) \tag{2.13}$$

NB: Only, for the I_{max} models (equation (2.7) and (2.8)) $A(t)$ is not added to $S(t)$ but S_0 is multiplied by $A(t)$ in the expression of $S(t)$. For instance, For I_{max} model with linear baseline we have

$$E(t) = S_0 * A(t) + k_{prog}t$$

2.1.3 Monolix model functions

Any combination of the 9 drug action models and 5 baseline/disease models is available in Monolix.

For instance, the combination of an E_{max} model for the drug action (2.5) and a constant baseline with no disease progression model (2.10) will result in the following equation:

$$E(t) = S_0 + \frac{E_{max}C(t)}{C(t) + C_{50}} \tag{2.14}$$

which corresponds to the model n°17: immed_Emax_const in the PD library (Appendix III).

As a second example, the combination of an I_{max} model for the drug action (2.7) with a linear progression as baseline/disease model (2.11) will give:

$$E(t) = S_0(1 - \frac{I_{max}C(t)}{C(t) + C_{50}}) + k_{prog}t \tag{2.15}$$

which corresponds to the model n°28: immed_Imax_lin.

The following table reports the name and numbers of the models.

Drug action models	Baseline/disease models: Null baseline	Constant baseline	Linear progression	Exponential increase	Exponential decrease
Linear	n°1: _lin_null	n°2: _lin_const	n°3: _lin_lin	n°4: _lin_exp	n°5: _lin_dexp
Quadratic	n°6: _quad_null	n°7: _quad_const	n°8: _quad_lin	n°9: _quad_exp	n°10: _quad_dexp
Logarithmic	n°11: _log_null	n°12: _log_const	n°13: _log_lin	n°14: _log_exp	n°15: _log_dexp
E_{max}	n°16: _Emax_null	n°17: _Emax_const	n°18: _Emax_lin	n°19: _Emax_exp	n°20: _Emax_dexp
Sigmoïd E_{max}	n°21: _gammaEmax_null	n°22: _gammaEmax_const	n°23: _gammaEmax_lin	n°24: _gammaEmax_exp	n°25: _gammaEmax_dexp
I_{max}	n°26: _Imax_null	n°27: _Imax_const	n°28: _Imax_lin	n°29: _Imax_exp	n°30: _Imax_dexp
Sigmoïd I_{max}	n°31: _gammaImax_null	n°32: _gammaImax_const	n°33: _gammaImax_lin	n°34: _gammaImax_exp	n°35: _gammaImax_dexp

Table 2.1: Immediate response model functions implemented in the Monolix library classed by drug action model (rows) and baseline/disease model (columns). The prefix immed has to be added to get the full name function

2.2 Turnover response models

In these models, the drug is not acting on the effect E directly but rather on R_{in} or k_{out} as represented in figure 2.1.

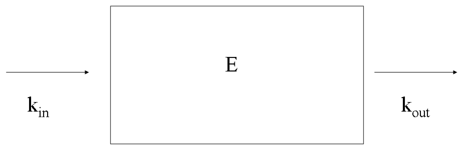

Figure 2.1: turnover model of the effect E

Thus the system is described with differential equations, given $\frac{dE}{dt}$ as a function of R_{in}, k_{out} and $C(t)$ the drug concentration at time t.

The initial condition is: while $C(t) = 0$, $E(t) = \frac{R_{in}}{k_{out}}$.

NB: In the version 2.4 of Monolix, turnover models of the library can only be linked to single dose PK models. An example using MLXTRAN for multiple doses is provided in the folder *my library*.

Parameters

- E_{max} = maximal agonistic response
- I_{max} = maximal antagonistic response
- C_{50} = concentration to get half of the maximal response (=drug potency)
- γ = sigmoidicity factor
- R_{in} = input (synthesis) rate
- k_{out} = output (elimination) rate constant

2.2.1 Models with impact on the input (R_{in})

- E_{max} model

$$\frac{dE}{dt} = R_{in}\left(1 + \frac{E_{max}C}{C + C_{50}}\right) - k_{out}E \tag{2.16}$$

Equation 2.16 corresponds to model n°36: turn_input_Emax.

- sigmoïd E_{max} model

$$\frac{dE}{dt} = R_{in}\left(1 + \frac{E_{max}C^{\gamma}}{C^{\gamma} + C_{50}^{\gamma}}\right) - k_{out}E \tag{2.17}$$

Equation 2.17 corresponds to model n°37: turn_input_gammaEmax.

- I_{max} model

$$\frac{dE}{dt} = R_{in}\left(1 - \frac{I_{max}C}{C + C_{50}}\right) - k_{out}E \tag{2.18}$$

Equation 2.18 corresponds to model n°38: turn_input_Imax.

- sigmoïd I_{max} model

$$\frac{dE}{dt} = R_{in}\left(1 - \frac{I_{max}C^{\gamma}}{C^{\gamma} + C_{50}^{\gamma}}\right) - k_{out}E \tag{2.19}$$

Equation 2.19 corresponds to model n°39: turn_input_gammaImax.

- full I_{max} model

$$\frac{dE}{dt} = R_{in}\left(1 - \frac{C}{C + C_{50}}\right) - k_{out}E \tag{2.20}$$

Equation 2.20 corresponds to model n°40: turn_input_Imaxfull.

- sigmoïd full I_{max} model

$$\frac{dE}{dt} = R_{in}\left(1 - \frac{C^{\gamma}}{C^{\gamma} + C_{50}^{\gamma}}\right) - k_{out}E \tag{2.21}$$

Equation 2.21 corresponds to model n°41: turn_input_gammaImaxfull.

2.2.2 Models with impact on the output (k_{out})

- E_{max} model

$$\frac{dE}{dt} = R_{in} - k_{out}\left(1 + \frac{E_{max}C}{C + C_{50}}\right)E \tag{2.22}$$

Equation 2.22 corresponds to model n°42: turn_output_Emax.

- sigmoïd E_{max} model

$$\frac{dE}{dt} = R_{in} - k_{out}\left(1 + \frac{E_{max}C^{\gamma}}{C^{\gamma} + C_{50}^{\gamma}}\right)E \tag{2.23}$$

Equation 2.23 corresponds to model n°43: turn_output_gammaEmax.

- I_{max} model

$$\frac{dE}{dt} = R_{in} - k_{out}\left(1 - \frac{I_{max}C}{C + C_{50}}\right)E \tag{2.24}$$

Equation 2.24 corresponds to model n°44: turn_output_Imax.

- sigmoïd I_{max} model

$$\frac{dE}{dt} = R_{in} - k_{out}\left(1 - \frac{I_{max}C^{\gamma}}{C^{\gamma} + C_{50}^{\gamma}}\right)E \tag{2.25}$$

Equation 2.25 corresponds to model n°45: turn_output_gammaImax.

- full I_{max} model

$$\frac{dE}{dt} = R_{in} - k_{out}\left(1 - \frac{C}{C + C_{50}}\right)E \tag{2.26}$$

Equation 2.26 corresponds to model n°46: turn_output_Imaxfull.

- sigmoïd full I_{max} model

$$\frac{dE}{dt} = R_{in} - k_{out}\left(1 - \frac{C^{\gamma}}{C^{\gamma} + C_{50}^{\gamma}}\right)E \tag{2.27}$$

Equation 2.27 corresponds to model n°47: turn_output_gammaImaxfull.

Appendix

List and names of the PK, PKe0 and PD models available in Monolix (version 2.4)

Appendix I: list of models in PK library

Library of PK Models (J. Bertrand and F. Mentré)
last release: 17/06/08

Model	Name	Input	n. cpt	Elimination	lag time	Parameterisation	Available		
							sd	md	ss
1	bolus_1cpt_Vk	IV-bolus	1	1st order	no	V,k	x	x	x
2	bolus_1cpt_VCl	IV-bolus	1	1st order	no	V,Cl	x	x	x
3	bolus_1cpt_VVmKm	IV-bolus	1	Michaelis-Menten	no	V,Vm,Km	x	x	
4	infusion_1cpt_Vk	IV-infusion	1	1st order	no	V,k	x	x	x
5	infusion_1cpt_VCl	IV-infusion	1	1st order	no	V,Cl	x	x	x
6	infusion_1cpt_VVmKm	IV-infusion	1	Michaelis-Menten	no	V,Vm,Km	x	x	
7	oral1_1cpt_kaVk	1st order	1	1st order	no	ka, V, k	x	x	x
8	oral1_1cpt_kaVCl	1st order	1	1st order	no	ka, V, Cl	x	x	x
9	oral1_1cpt_kaVVmKm	1st order	1	Michaelis-Menten	no	ka, V, Vm, Km	x	x	
10	oral1_1cpt_TlagkaVk	1st order	1	1st order	yes	Tlag, ka, V, k	x	x	x
11	oral1_1cpt_TlagkaVCl	1st order	1	1st order	yes	Tlag, ka, V, Cl	x	x	x
12	oral1_1cpt_TlagkaVVmKm	1st order	1	Michaelis-Menten	yes	Tlag, ka, V, Vm, Km	x	x	
13	oral0_1cpt_Tk0Vk	0 order	1	1st order	no	Tk0,V,k	x	x	x
14	oral0_1cpt_Tk0VCl	0 order	1	1st order	no	Tk0,V,Cl	x	x	x
15	oral0_1cpt_Tk0VVmKm	0 order	1	Michaelis-Menten	no	Tk0,V,Vm,Km	x	x	
16	oral0_1cpt_TlagTk0Vk	0 order	1	1st order	yes	Tlag, Tk0,V,k	x	x	x
17	oral0_1cpt_TlagTk0VCl	0 order	1	1st order	yes	Tlag, Tk0,V,Cl	x	x	x
18	oral0_1cpt_TlagTk0VVmKm	0 order	1	Michaelis-Menten	yes	Tlag, Tk0,V,Vm, Km	x	x	

19	bolus_2cpt_Vkk12k21	IV-bolus	2	1st order	no	V, k, k12, k21	x	x	x
20	bolus_2cpt_ClV1QV2	IV-bolus	2	1st order	no	Cl, V1, Q, V2	x	x	x
21	bolus_2cpt_alphabetaAB	IV-bolus	2	1st order	no	alpha, beta, A, B	x	x	x
22	bolus_2cpt_Vk12k21VmKm	IV-bolus	2	Michaelis-Menten	no	V, k12, k21, Vm, Km	x	x	
23	bolus_2cpt_V1QV2VmKm	IV-bolus	2	Michaelis-Menten	no	V1, Q, V2, Vm, Km	x	x	
24	infusion_2cpt_Vkk12k21	IV-infusion	2	1st order	no	V, k, k12, k21	x	x	x
25	infusion_2cpt_ClV1QV2	IV-infusion	2	1st order	no	Cl, V1, Q, V2	x	x	x
26	infusion_2cpt_alphabetaAB	IV-infusion	2	1st order	no	alpha, beta, A, B	x	x	x
27	infusion_2cpt_Vk12k21VmKm	IV-infusion	2	Michaelis-Menten	no	V, k12, k21, Vm, Km	x	x	
28	infusion_2cpt_V1QV2VmKm	IV-infusion	2	Michaelis-Menten	no	V1, Q, V2, Vm,Km	x	x	
29	oral1_2cpt_kaVkk12k21	1st order	2	1st order	no	ka,V, k, k12, k21	x	x	x
30	oral1_2cpt_kaClV1QV2	1st order	2	1st order	no	ka, Cl, V1, Q, V2	x	x	x
31	oral1_2cpt_kaalphabetaAB	1st order	2	1st order	no	ka, alpha, beta, A, B	x	x	x
32	oral1_2cpt_kaVk12k21VmKm	1st order	2	Michaelis-Menten	no	ka,V, k12, k21, Km, Vm	x	x	
33	oral1_2cpt_kaV1QV2VmKm	1st order	2	Michaelis-Menten	no	ka, V1, Q, V2, Km, Vm	x	x	
34	oral1_2cpt_TlagkaVkk12k21	1st order	2	1st order	yes	Tlag, ka,V, k, k12, k21	x	x	x
35	oral1_2cpt_TlagkaClV1QV2	1st order	2	1st order	yes	Tlag, ka, Cl, V1, Q, V2	x	x	x
36	oral1_2cpt_TlagkaalphabetaAB	1st order	2	1st order	yes	Tlag, ka, alpha, beta, A, B	x	x	x
37	oral1_2cpt_TlagkaVk12k21VmKm	1st order	2	Michaelis-Menten	yes	Tlag, ka, V, k12, k21, Km, Vm	x	x	
38	oral1_2cpt_TlagkaV1QV2VmKm	1st order	2	Michaelis-Menten	yes	Tlag, ka, V1, Q, V2, Vm, Km	x	x	
39	oral0_2cpt_Tk0Vkk12k21	0 order	2	1st order	no	Tk0, V, k, k12, k21	x	x	x
40	oral0_2cpt_Tk0ClV1QV2	0 order	2	1st order	no	Tk0, Cl, V1, Q, V2	x	x	x
41	oral0_2cpt_Tk0alphabetaAB	0 order	2	1st order	no	Tk0, alpha, beta, A, B	x	x	x
42	oral0_2cpt_Tk0Vk12k21VmKm	0 order	2	Michaelis-Menten	no	Tk0,V, k12, k21, Km, Vm	x	x	
43	oral0_2cpt_Tk0V1QV2VmKm	0 order	2	Michaelis-Menten	no	Tk0, V1, Q, V2, Km, Vm	x	x	
44	oral0_2cpt_TlagTk0Vkk12k21	0 order	2	1st order	yes	Tlag, Tk0, V, k, k12, k21	x	x	x
45	oral0_2cpt_TlagTk0ClV1QV2	0 order	2	1st order	yes	Tlag, Tk0, Cl, V1, Q, V2	x	x	x
46	oral0_2cpt_TlagTk0alphabetaAB	0 order	2	1st order	yes	Tlag, Tk0, alpha, beta, A, B	x	x	x
47	oral0_2cpt_TlagTk0Vk12k21VmKm	0 order	2	Michaelis-Menten	yes	Tlag, Tk0,V, k12, k21, Km, Vm	x	x	
48	oral0_2cpt_TlagTk0V1QV2VmKm	0 order	2	Michaelis-Menten	yes	Tlag, Tk0, V1, Q, V2, Km, Vm	x	x	

49	bolus_3cpt_Vkk12k21k13k31	IV-bolus	3	1st order	no	V, k, k12, k21, k13, k31	x	x	x
50	bolus_3cpt_ClV1Q2V2Q3V3	IV-bolus	3	1st order	no	Cl, V1, Q2, V2, Q3, V3	x	x	x
51	bolus_3cpt_alphabetagammaABC	IV-bolus	3	1st order	no	alpha, beta, gamma, A, B, C	x	x	x
52	bolus_3cpt_Vk12V12k13k31VmKm	IV-bolus	3	Michaelis-Menten	no	V, k12, k21, k13, k31, Vm, Km	x	x	
53	bolus_3cpt_V1Q2V2Q3V3VmKm	IV-bolus	3	Michaelis-Menten	no	V1, Q2, V2, Q3, V3, Vm, Km	x	x	
54	infusion_3cpt_Vkk12k21k13k31	IV-infusion	3	1st order	no	V, k, k12, k21, k13, k31	x	x	x
55	infusion_3cpt_ClV1Q2V2Q3V3	IV-infusion	3	1st order	no	Cl, V1, Q2, V2, Q3, V3	x	x	x
56	infusion_3cpt_alphabetagammaABC	IV-infusion	3	1st order	no	alpha, beta, gamma, A, B, C	x	x	x
57	infusion_3cpt_Vk12V12k13k31VmKm	IV-infusion	3	Michaelis-Menten	no	V, k12, k21, k13, k31, Vm, Km	x	x	
58	infusion_3cpt_V1Q2V2Q3V3VmKm	IV-infusion	3	Michaelis-Menten	no	V1, Q2, V2, Q3, V3, Vm, Km	x	x	
59	oral1_3cpt_kaVkk12k21k13k31	1st order	3	1st order	no	ka, V, k, k12, k21, k13, k31	x	x	x
60	oral1_3cpt_kaClV1Q2V2Q3V3	1st order	3	1st order	no	ka, Cl, V1, Q2, V2, Q3, V3	x	x	x
61	oral1_3cpt_kaalphabetagammaABC	1st order	3	1st order	no	ka, alpha, beta, gamma, A, B, C	x	x	x
62	oral1_3cpt_kaVk12V12k13k31VmKm	1st order	3	Michaelis-Menten	no	ka,V, k12, k21, k13, k31, Vm, Km	x	x	
63	oral1_3cpt_kaV1Q2V2Q3V3VmKm	1st order	3	Michaelis-Menten	no	ka, V1, Q2, V2, Q3, V3, Vm, Km	x	x	
64	oral1_3cpt_TlagkaVkk12k21k13k31	1st order	3	1st order	yes	Tlag, ka, V, k, k12, k21, k13, k31	x	x	x
65	oral1_3cpt_TlagkaClV1Q2V2Q3V3	1st order	3	1st order	yes	Tlag, ka, Cl, V1, Q2, V2, Q3, V3	x	x	x
66	oral1_3cpt_TlagkaalphabetagammaABC	1st order	3	1st order	yes	Tlag, ka, alpha, beta, gamma, A, B, C	x	x	x
67	oral1_3cpt_TlagkaVk12V12k13k31VmKm	1st order	3	Michaelis-Menten	yes	Tlag, ka, V, k12, k21, k13, k31, Vm, Km	x	x	
68	oral1_3cpt_TlagkaV1Q2V2Q3V3VmKm	1st order	3	Michaelis-Menten	yes	Tlag, ka, V1, Q2, V2, Q3, V3, Vm, Km	x	x	
69	oral0_3cpt_Tk0Vkk12k21k13k31	0 order	3	1st order	no	Tk0, V, k, k12, k21, k13, k31	x	x	x
70	oral0_3cpt_Tk0ClV1Q2V2Q3V3	0 order	3	1st order	no	Tk0, Cl, V1, Q2, V2, Q3, V3	x	x	x
71	oral0_3cpt_Tk0alphabetagammaABC	0 order	3	1st order	no	Tk0, alpha, beta, gamma, A, B, C	x	x	x
72	oral0_3cpt_Tk0Vk12V12k13k31VmKm	0 order	3	Michaelis-Menten	no	Tk0, V, k12, k21, k13, k31, Vm, Km	x	x	
73	oral0_3cpt_Tk0V1Q2V2Q3V3VmKm	0 order	3	Michaelis-Menten	no	Tk0, V1, Q2, V2, Q3, V3, Vm, Km	x	x	
74	oral0_3cpt_TlagTk0Vkk12k21k13k31	0 order	3	1st order	yes	Tlag, Tk0, V, k, k12, k21, k13, k31	x	x	x
75	oral0_3cpt_TlagTk0ClV1Q2V2Q3V3	0 order	3	1st order	yes	Tlag, Tk0, Cl, V1, Q2, V2, Q3, V3	x	x	x
76	oral0_3cpt_TlagTk0alphabetagammaABC	0 order	3	1st order	yes	Tlag, Tk0, alpha, beta, gamma, A, B, C	x	x	x
77	oral0_3cpt_TlagTk0Vk12V12k13k31VmKm	0 order	3	Michaelis-Menten	yes	Tlag, Tk0, V, k12, k21, k13, k31, Vm, Km	x	x	
78	oral0_3cpt_TlagTk0V1Q2V2Q3V3VmKm	0 order	3	Michaelis-Menten	yes	Tlag, Tk0, V1, Q2, V2, Q3, V3, Vm, Km	x	x	

Appendix II: list of models in PKe0 library

Library of PKe0 Models (J. Bertrand and F. Mentré)
last release: 15/09/08

Model	Name	Input	n. cpt	Elimination	lag time	Parameterisation	sd	Available md	ss
1	bolus_1cpt_Vkke0	IV-bolus	1	1st order	no	V,k,ke0	x	x	x
2	bolus_1cpt_VClke0	IV-bolus	1	1st order	no	V,Cl,ke0	x	x	x
3	bolus_1cpt_VVmKmke0	IV-bolus	1	Michaelis-Menten	no	V,Vm,Km,ke0	x	x	
4	infusion_1cpt_Vkke0	IV-infusion	1	1st order	no	V,k,ke0	x	x	x
5	infusion_1cpt_VClke0	IV-infusion	1	1st order	no	V,Cl,ke0	x	x	x
6	infusion_1cpt_VVmKmke0	IV-infusion	1	Michaelis-Menten	no	V,Vm,Km,ke0	x	x	
7	oral1_1cpt_kaVkke0	1st order	1	1st order	no	ka,V,k,ke0	x	x	x
8	oral1_1cpt_kaVClke0	1st order	1	1st order	no	ka,V,Cl,ke0	x	x	x
9	oral1_1cpt_kaVVmKmke0	1st order	1	Michaelis-Menten	no	ka,V,Vm,Km,ke0	x	x	
10	oral1_1cpt_TlagkaVkke0	1st order	1	1st order	yes	Tlag,ka,V,k,ke0	x	x	x
11	oral1_1cpt_TlagkaVClke0	1st order	1	1st order	yes	Tlag, ka, V, Cl, ke0	x	x	x
12	oral1_1cpt_TlagkaVVmKmke0	1st order	1	Michaelis-Menten	yes	Tlag, ka, V, Vm, Km, ke0	x	x	
13	oral0_1cpt_Tk0Vkke0	0 order	1	1st order	no	Tk0,V,k,ke0	x	x	x
14	oral0_1cpt_Tk0VClke0	0 order	1	1st order	no	Tk0,V,Cl,ke0	x	x	x
15	oral0_1cpt_Tk0VVmKmke0	0 order	1	Michaelis-Menten	no	Tk0,V,Vm, Km,ke0	x	x	
16	oral0_1cpt_TlagTk0Vkke0	0 order	1	1st order	yes	Tlag, Tk0,V,k,ke0	x	x	x
17	oral0_1cpt_TlagTk0VClke0	0 order	1	1st order	yes	Tlag, Tk0,V,Cl,ke0	x	x	x
18	oral0_1cpt_TlagTk0VVmKmke0	0 order	1	Michaelis-Menten	yes	Tlag, Tk0,V,Vm, Km,ke0	x	x	

19	bolus_2cpt_Vkk12k21ke0	IV-bolus	2	1st order	no	V, k, k12, k21, ke0	x	x	x
20	bolus_2cpt_ClV1QV2ke0	IV-bolus	2	1st order	no	Cl, V1, Q, V2, ke0	x	x	x
21	bolus_2cpt_alphabetaABke0	IV-bolus	2	1st order	no	alpha, beta, A, B, ke0	x	x	x
22	bolus_2cpt_Vk12k21VmKmke0	IV-bolus	2	Michaelis-Menten	no	V, k12, k21, Vm, Km, ke0	x	x	
23	bolus_2cpt_V1QV2VmKmke0	IV-bolus	2	Michaelis-Menten	no	V1, Q, V2, Vm, Km, ke0	x	x	
						, ke0			
24	infusion_2cpt_Vkk12k21ke0	IV-infusion	2	1st order	no	V, k, k12, k21, ke0	x	x	x
25	infusion_2cpt_ClV1QV2ke0	IV-infusion	2	1st order	no	Cl, V1, Q, V2, ke0	x	x	x
26	infusion_2cpt_alphabetaABke0	IV-infusion	2	1st order	no	alpha, beta, A, B, ke0	x	x	x
27	infusion_2cpt_Vk12k21VmKmke0	IV-infusion	2	Michaelis-Menten	no	V, k12, k21, Vm, Km, ke0	x	x	
28	infusion_2cpt_V1QV2VmKmke0	IV-infusion	2	Michaelis-Menten	no	V1, Q, V2, Vm,Km, ke0	x	x	
						, ke0			
29	oral1_2cpt_kaVkk12k21ke0	1st order	2	1st order	no	ka,V, k, k12, k21, ke0	x	x	x
30	oral1_2cpt_kaClV1QV2ke0	1st order	2	1st order	no	ka, Cl, V1, Q, V2, ke0	x	x	x
31	oral1_2cpt_kaalphabetaABke0	1st order	2	1st order	no	ka, alpha, beta, A, B, ke0	x	x	x
32	oral1_2cpt_kaVk12k21VmKmke0	1st order	2	Michaelis-Menten	no	ka,V, k12, k21, Km, Vm, ke0	x	x	
33	oral1_2cpt_kaV1QV2VmKmke0	1st order	2	Michaelis-Menten	no	ka, V1, Q, V2, Km, Vm, ke0	x	x	
34	oral1_2cpt_TlagkaVkk12k21ke0	1st order	2	1st order	yes	Tlag, ka,V, k, k12, k21, ke0	x	x	x
35	oral1_2cpt_TlagkaClV1QV2ke0	1st order	2	1st order	yes	Tlag, ka, Cl, V1, Q, V2, ke0	x	x	x
36	oral1_2cpt_TlagkaalphabetaABke0	1st order	2	1st order	yes	Tlag, ka, alpha, beta, A, B, ke0	x	x	x
37	oral1_2cpt_TlagkaVk12k21VmKmke0	1st order	2	Michaelis-Menten	yes	Tlag, ka, V, k12, k21, Km, Vm, ke0	x	x	
38	oral1_2cpt_TlagkaV1QV2VmKmke0	1st order	2	Michaelis-Menten	yes	Tlag, ka, V1, Q, V2, Vm, Km, ke0	x	x	
						, ke0			
39	oral0_2cpt_Tk0Vkk12k21ke0	0 order	2	1st order	no	Tk0, V, k, k12, k21, ke0	x	x	x
40	oral0_2cpt_Tk0ClV1QV2ke0	0 order	2	1st order	no	Tk0, Cl, V1, Q, V2, ke0	x	x	x
41	oral0_2cpt_Tk0alphabetaABke0	0 order	2	1st order	no	Tk0, alpha, beta, A, B, ke0	x	x	x
42	oral0_2cpt_Tk0Vk12k21VmKmke0	0 order	2	Michaelis-Menten	no	Tk0,V, k12, k21, Km, Vm, ke0	x	x	
43	oral0_2cpt_Tk0V1QV2VmKmke0	0 order	2	Michaelis-Menten	no	Tk0, V1, Q, V2, Km, Vm, ke0	x	x	
44	oral0_2cpt_TlagTk0Vkk12k21ke0	0 order	2	1st order	yes	Tlag, Tk0, V, k, k12, k21, ke0	x	x	x
45	oral0_2cpt_TlagTk0ClV1QV2ke0	0 order	2	1st order	yes	Tlag, Tk0, Cl, V1, Q, V2, ke0	x	x	x
46	oral0_2cpt_TlagTk0alphabetaABke0	0 order	2	1st order	yes	Tlag, Tk0, alpha, beta, A, B, ke0	x	x	x
47	oral0_2cpt_TlagTk0Vk12k21VmKmke0	0 order	2	Michaelis-Menten	yes	Tlag, Tk0,V, k12, k21, Km, Vm, ke0	x	x	
48	oral0_2cpt_TlagTk0V1QV2VmKmke0	0 order	2	Michaelis-Menten	yes	Tlag, Tk0, V1, Q, V2, Km, Vm, ke0	x	x	

Appendix III: list of models in PD library

Library of PD Models (J. Bertrand and F. Mentré)
last release: 17/06/08

Model	Name	Link to PK	Type of response	Drug action model	Baseline/disease model	Parameterisation	Available
1	immed_lin_null	optional	immediate	linear	null	Alin	x
2	immed_lin_const	optional	immediate	linear	constant	Alin, S0	x
3	immed_lin_lin	optional	immediate	linear	linear	Alin, kprog, S0	x
4	immed_lin_exp	optional	immediate	linear	exponential	Alin, kprog, S0	x
5	immed_lin_dexp	optional	immediate	linear	exponential decreasing	Alin, kprog, S0	x
6	immed_quad_null	optional	immediate	quadratic	null	Aquad, Alin	x
7	immed_quad_const	optional	immediate	quadratic	constant	Aquad, Alin, S0	x
8	immed_quad_lin	optional	immediate	quadratic	linear	Aquad, Alin, kprog, S0	x
9	immed_quad_exp	optional	immediate	quadratic	exponential	Aquad, Alin, kprog, S0	x
10	immed_quad_dexp	optional	immediate	quadratic	exponential decreasing	Aquad, Alin, kprog, S0	x
11	immed_log_null	optional	immediate	logarithmic	null	Alog	x
12	immed_log_const	optional	immediate	logarithmic	constant	Alog, S0	x
13	immed_log_lin	optional	immediate	logarithmic	linear	Alog, kprog, S0	x
14	immed_log_exp	optional	immediate	logarithmic	exponential	Alog, kprog, S0	x
15	immed_log_dexp	optional	immediate	logarithmic	exponential decreasing	Alog, kprog, S0	x
16	immed_Emax_null	optional	immediate	Emax	null	Emax, C50	x
17	immed_Emax_const	optional	immediate	Emax	constant	Emax, C50, S0	x
18	immed_Emax_lin	optional	immediate	Emax	linear	Emax, C50, kprog, S0	x
19	immed_Emax_exp	optional	immediate	Emax	exponential	Emax, C50, kprog, S0	x
20	immed_Emax_dexp	optional	immediate	Emax	exponential decreasing	Emax, C50, kprog, S0	x
21	immed_gammaEmax_null	optional	immediate	sigmoid Emax	null	gamma, Emax, C50	x
22	immed_gammaEmax_const	optional	immediate	sigmoid Emax	constant	gamma, Emax, C50, S0	x
23	immed_gammaEmax_lin	optional	immediate	sigmoid Emax	linear	gamma, Emax, C50, kprog, S0	x
24	immed_gammaEmax_exp	optional	immediate	sigmoid Emax	exponential	gamma, Emax, C50, kprog, S0	x
25	immed_gammaEmax_dexp	optional	immediate	sigmoid Emax	exponential decreasing	gamma, Emax, C50, kprog, S0	x

26	immed_Imax_null[a]	optional	immediate	Imax	null	Imax, C50	x
27	immed_Imax_const[a]	optional	immediate	Imax	constant	Imax, C50, S0	x
28	immed_Imax_lin[a]	optional	immediate	Imax	linear	Imax, C50, kprog, S0	x
29	immed_Imax_exp[a]	optional	immediate	Imax	exponential	Imax, C50, kprog, S0	x
30	immed_Imax_dexp[a]	optional	immediate	Imax	exponential decreasing	Imax, C50, kprog, S0	x
31	immed_gammaImax_null[a]	optional	immediate	sigmoid Imax	null	gamma, Imax, C50	x
32	immed_gammaImax_const[a]	optional	immediate	sigmoid Imax	constant	gamma, Imax, C50, S0	x
33	immed_gammaImax_lin[a]	optional	immediate	sigmoid Imax	linear	gamma, Imax, C50, kprog, S0	x
34	immed_gammaImax_exp[a]	optional	immediate	sigmoid Imax	exponential	gamma, Imax, C50, kprog, S0	x
35	immed_gammaImax_dexp[a]	optional	immediate	sigmoid Imax	exponential decreasing	gamma, Imax, C50, kprog, S0	x
36	turn_input_Emax[b]	required	turnover	Emax/input	Rin/kout	Rin, kout, Emax, C50	x
37	turn_input_gammaEmax[b]	required	turnover	sigmoid Emax/input	Rin/kout	gamma, Rin, kout, Emax, C50	x
38	turn_input_Imax[b]	required	turnover	Imax/input	Rin/kout	Rin, kout, Imax, C50	x
39	turn_input_gammaImax[b]	required	turnover	sigmoid Imax/input	Rin/kout	gamma, Rin, kout, Imax, C50	x
40	turn_input_Imaxfull[b,c]	required	turnover	full Imax/input	Rin/kout	Rin, kout, C50	x
41	turn_input_gammaImaxfull[b,c]	required	turnover	sigmoid full Imax/input	Rin/kout	gamma, Rin, kout, C50	x
42	turn_output_Emax[b]	required	turnover	Emax/output	Rin/kout	Rin, kout, Emax, C50	x
43	turn_output_gammaEmax[b]	required	turnover	sigmoid Emax/output	Rin/kout	gamma, Rin, kout, Emax, C50	x
44	turn_output_Imax[b]	required	turnover	Imax/ouput	Rin/kout	Rin, kout, Imax, C50	x
45	turn_output_gammaImax[b]	required	turnover	sigmoid Imax/ouput	Rin/kout	gamma, Rin, kout, Imax, C50	x
46	turn_output_Imaxfull[b,c]	required	turnover	full Imax/ouput	Rin/kout	Rin, kout, C50	x
47	turn_output_gammaImaxfull[b,c]	required	turnover	sigmoid full Imax/ouput	Rin/kout	gamma, Rin, kout, C50	x

[a] for Imax direct response models, drug effect is acting on baseline S0 through a product

[b] Available only for single dose PK

[c] full Imax means Imax is fixed equal to 1