PFIM 4.0

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www.pfim.biostat.fr

Library of Model

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PFIM 4.0 is free library of functions.
The Université Paris Diderot and INSERM are the co-owners of this library of functions.

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The library of pharmacokinetic (PK) and pharmacodynamic (PD) models described in this document is implemented in the PFIM software since version 3.2.1 and in PFIM Interface since version 3.1 (www.pfim.biostat.fr). The PK/PD libraries of PFIM are derived from the PK/PD models implemented in the Monolix software and described by Julie Bertrand and France Mentré in a Monolix software documentation (software.monolix.org). PFIM is a free library of functions. The University Paris Diderot and INSERM are the co-owners of this library of functions (version 3.2, copyright 2010).

Contents

Chapter 1

Pharmacokinetic models

The equations in the ensuing chapter describe the pharmacokinetic models implemented in the PFIM software (www.pfim.biostat.fr). The presentation of the models is organised as follows:

- First level: elimination process
  - Linear
  - Michaelis-Menten
- Second level: number of compartments
  - One compartment
  - Two compartments
  - Three compartments
- Third level: route of administration
  - Intravenous bolus
  - Infusion
  - Oral (first order absorption)
- 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 $(t \geq t_D)$
- Multiple 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 *(only for linear elimination)*: at a time t after dose D given at time t_D after repeated administration of dose D given at interval τ $(t \geq t_D)$

NB: For infusion, the duration of infusion is $Tinf$ for single dose and $Tinf_i$ $(i = 1, ...n)$ for multiple doses. D is the total administered dose for single dose; D_i is the total i^{th} administered dose for multiple doses.

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

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

1.1 Compartmental models and parameters

In the ensuing section, the mammillary models with one, two or three compartments are presented with the associated parameters and the different parameterisations. Six parameters are common to one, two or three compartment models:

- V or V_1, the volume of distribution in the central compartment
- k, the elimination rate constant
- CL, the clearance of elimination
- V_m, the maximum elimination rate for Michaelis-Menten elimination
- K_m, the Michaelis-Menten constant
- k_a, the absorption rate constant for oral administration

NB: Since PFIM4.0, V_m is in concentration per time unit and K_m is in concentration unit.

1.1.1 One-compartment models

The one-compartment model implemented in PFIM is described in Figure 1.1.

Figure 1.1: A mammillary model with one compartment, parameterized in micro-constant $V$and k (a) or with CL and V (b).

There are two parameterisations implemented in PFIM for one-compartment models, (V and k) or (V and CL). The equations are given for the first parameterisation (V, k). For extra-vascular administration, V and CL are apparent volume and clearance.
The equations for the second parameterisation (V, CL) are derived using $k = \dfrac{CL}{V}$.

1.1.2 Two-compartment models

The two-compartment model implemented in PFIM is described in Figure 1.2. For two-compartment model equations, $C(t) = C_1(t)$ represent the drug concentration in the first compartment and $C_2(t)$ represents the drug concentration in the second compartment.

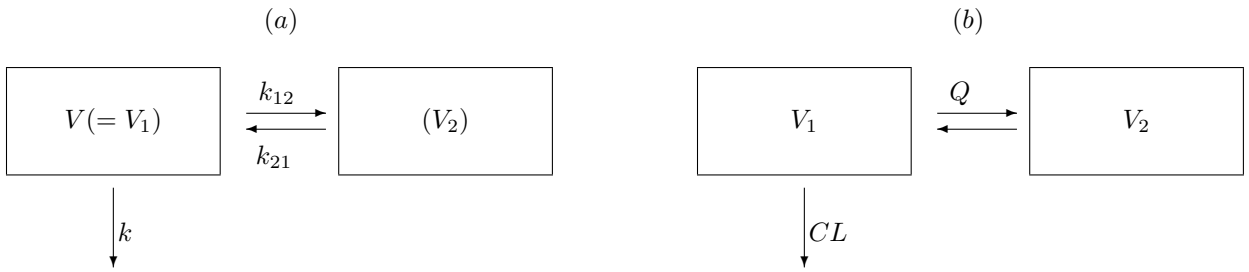

Figure 1.2: A mammillary model with two compartments, parameterized in micro-constants V, k, k_{12} and k_{21} (a) or with CL, V_1, Q and V_2 (b)

As well as the previously described PK parameters, the following PK parameters are used for the two-compartment models:

- V_2, the volume of distribution of second compartment
- k_{12}, the distribution rate constant from compartment 1 to compartment 2
- k_{21}, the distribution rate constant from compartment 2 to compartment 1
- Q, the inter-compartmental clearance

There are two parameterisations implemented in PFIM for two-compartment models: (V, k, k_{12} and k_{21}), or (CL, V_1, Q and V_2). For extra-vascular administration, V_1 (V), V_2, CL, and Q are apparent volumes and clearances.

The second parameterisation terms are derived using:

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

1.1.3 Three-compartment models

The three-compartment model implemented in PFIM is described in Figure 1.3. For three-compartment model equations, $C(t) = C_1(t)$ represent the drug concentration in the first compartment, $C_2(t)$ represents the drug concentration in the second compartment, and $C_3(t)$ represents the drug concentration in the third compartment.

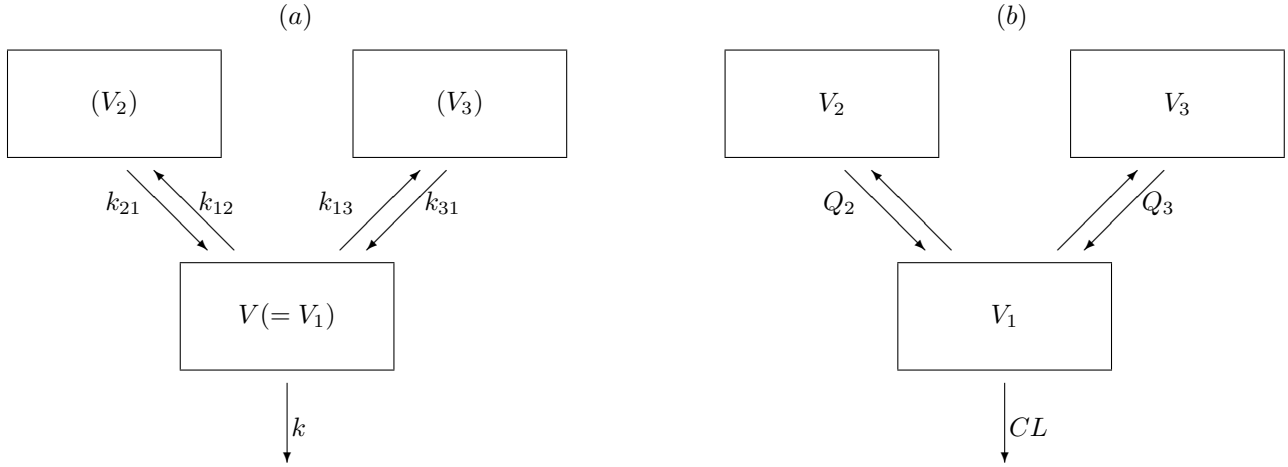

Figure 1.3: A mammillary model with three compartments parameterized in micro-constants V, k, k_{12}, k_{21}, k_{13} and k_{31} (a) or with CL, V_1, Q_2, V_2, Q_3 and V_3 (b)

As well as the previously described PK parameters, the following PK parameters are used for the three-compartment models:

- V_3, the volume of distribution of third compartment
- k_{13}, the distribution rate constant from compartment 1 to compartment 3
- k_{31}, the distribution rate constant from compartment 3 to compartment 1

- Q_2 (=Q), the inter-compartmental clearance from compartment 1 to compartment 2
- Q_3, the inter-compartmental clearance from compartment 1 to compartment 3

There are two parameterisations implemented in PFIM for three-compartment models: (V, k, k_{12}, k_{21}, k_{13} and k_{31}), or (CL, V_1, Q_2, V_2, Q_3 and V_3). For extra-vascular administration, V_1 (V), V_2, V_3, CL, Q_2, and Q_3 are apparent volumes and clearances.

The second parameterisation terms are derived using:

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

NB: For models with Michaelis-Menten elimination the elimination parameter is not k (or CL) but V_m and K_m for both parameterisations of one, two or three-compartment models.

1.2 Models with linear elimination

The list of PK models with linear elimination implemented in PFIM are summarised in Appendix I.1.

1.2.1 One-compartment models

1.2.1.1 Intravenous bolus

- single dose

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

- multiple doses

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

- steady state

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

1.2.1.2 Infusion

- single dose

$$C(t) = \begin{cases} \dfrac{D}{Tinf}\dfrac{1}{kV}\left(1 - e^{-k(t-t_D)}\right) & \text{if } t - t_D \leq Tinf, \\ \dfrac{D}{Tinf}\dfrac{1}{kV}\left(1 - e^{-kTinf}\right)e^{-k(t-t_D-Tinf)} & \text{if not.} \end{cases} \tag{1.4}$$

- multiple doses

$$C(t) = \begin{cases} \displaystyle\sum_{i=1}^{n-1} \frac{D_i}{Tinf_i}\frac{1}{kV}\left(1 - e^{-kTinf_i}\right)e^{-k\left(t-t_{D_i}-Tinf_i\right)} & \\ \qquad + \dfrac{D_n}{Tinf_n}\dfrac{1}{kV}\left(1 - e^{-k(t-t_{D_n})}\right) & \text{if } t - t_{D_n} \leq Tinf_n, \\ \displaystyle\sum_{i=1}^{n} \frac{D_i}{Tinf_i}\frac{1}{kV}\left(1 - e^{-kTinf_i}\right)e^{-k\left(t-t_{D_i}-Tinf_i\right)} & \text{if not.} \end{cases} \tag{1.5}$$

- steady state

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

1.2.1.3 First order absorption

- single dose

$$C(t) = \frac{D}{V}\frac{k_a}{k_a - k}\left(e^{-k(t-t_D)} - e^{-k_a(t-t_D)}\right) \tag{1.7}$$

- multiple doses

$$C(t) = \sum_{i=1}^{n} \frac{D_i}{V}\frac{k_a}{k_a - k}\left(e^{-k\left(t-t_{D_i}\right)} - e^{-k_a\left(t-t_{D_i}\right)}\right) \tag{1.8}$$

- steady state

$$C(t) = \frac{D}{V}\frac{k_a}{k_a - k}\left(\frac{e^{-k(t-t_D)}}{1 - e^{-k\tau}} - \frac{e^{-k_a(t-t_D)}}{1 - e^{-k_a\tau}}\right) \tag{1.9}$$

NB: Equations 1.1 to 1.9 correspond to models n°1 to n°6 in Appendix I.1.

1.2.2 Two-compartment models

For readability, the equations for two-compartment models with linear elimination are given using the variables α, β, A and B defined by the following expressions:

- $\alpha = \dfrac{k_{21}k}{\beta} = \dfrac{\dfrac{Q}{V_2}\dfrac{CL}{V_1}}{\beta}$

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

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

1.2.2.1 Intravenous bolus

For intravenous bolus, the link between A and B, and the parameters (V, k, k_{12} and k_{21}), or (CL, V_1, Q and V_2) is defined as follows:

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

- single dose

$$C(t) = D\left(Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)}\right) \tag{1.10}$$

- multiple doses

$$C(t) = \sum_{i=1}^{n} D_i\left(Ae^{-\alpha\left(t-t_{D_i}\right)} + Be^{-\beta\left(t-t_{D_i}\right)}\right) \tag{1.11}$$

- steady state

$$C(t) = D\left(\frac{Ae^{-\alpha t}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta t}}{1-e^{-\beta\tau}}\right) \tag{1.12}$$

1.2.2.2 Infusion

For infusion, the link between A and B, and the parameters (V, k, k_{12} and k_{21}), or (CL, V_1, Q and V_2) is defined as follows:

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

- single dose

$$C(t) = \begin{cases} \frac{D}{Tinf}\left[\begin{array}{l} \frac{A}{\alpha}\left(1-e^{-\alpha(t-t_D)}\right) \\ +\frac{B}{\beta}\left(1-e^{-\beta(t-t_D)}\right) \end{array}\right] & \text{if } t-t_D \leq Tinf, \\ \frac{D}{Tinf}\left[\begin{array}{l} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.13}$$

- multiple doses

$$C(t) = \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{Tinf_i} \left[\begin{array}{l} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \end{array} \right] & \\ \quad + \frac{D}{Tinf_n} \left[\begin{array}{l} \frac{A}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\frac{B}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \end{array} \right] & \text{if } t-t_{D_n} \leq Tinf, \\ \sum_{i=1}^{n} \frac{D_i}{Tinf_i} \left[\begin{array}{l} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \end{array} \right] & \text{if not.} \end{cases} \tag{1.14}$$

- steady state

$$C(t) = \begin{cases} \frac{D}{Tinf} \left[\begin{array}{l} \frac{A}{\alpha}\left(\begin{array}{l} \left(1-e^{-\alpha(t-t_D)}\right) \\ +e^{-\alpha\tau}\frac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}} \end{array} \right) \\ +\frac{B}{\beta}\left(\begin{array}{l} \left(1-e^{-\beta(t-t_D)}\right) \\ +e^{-\beta\tau}\frac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}} \end{array} \right) \end{array} \right] & \text{if } t-t_D \leq Tinf, \\ \frac{D}{Tinf} \left[\begin{array}{l} \frac{A}{\alpha}\left(\frac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}} \right) \\ +\frac{B}{\beta}\left(\frac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}} \right) \end{array} \right] & \text{if not.} \end{cases} \tag{1.15}$$

1.2.2.3 First order absorption

For first order absorption, the link between A and B, and the parameters (k_a, V, k, k_{12} and k_{21}), or (k_a, CL, V_1, Q and V_2) is defined as follows:

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

- single dose

$$C(t) = D\left(Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)} - (A+B)e^{-k_a(t-t_D)}\right) \tag{1.16}$$

- multiple doses

$$C(t) = \sum_{i=1}^{n} D_i\left(Ae^{-\alpha\left(t-t_{D_i}\right)} + Be^{-\beta\left(t-t_{D_i}\right)} - (A+B)e^{-k_a\left(t-t_{D_i}\right)}\right) \tag{1.17}$$

- steady state

$$C(t) = D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}} - \frac{(A+B)e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \tag{1.18}$$

NB: Equations 1.10 to 1.18 correspond to models n°7 to n°12 in Appendix I.1.

1.2.3 Three-compartment models

For readability, the equations for three-compartment models with linear elimination are given using the variables α, β, γ, A, B and C defined by the following expressions:

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

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

1.2.3.1 Intravenous bolus

For intravenous bolus, the link between A B, and C, and the parameters (V, k, k_{12}, k_{21}, k_{13} and k_{31}), or (CL, V_1, Q_2, V_2, Q_3 and V_3) is defined as follows:

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

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

- single dose

$$C(t) = D\left(Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)} + Ce^{-\gamma(t-t_D)}\right) \tag{1.19}$$

- multiple doses

$$C(t) = \sum_{i=1}^{n} D_i\left(Ae^{-\alpha(t-tD_i)} + Be^{-\beta(t-tD_i)} + Ce^{-\gamma(t-tD_i)}\right) \tag{1.20}$$

- steady state

$$C(t) = D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}} + \frac{Ce^{-\gamma(t-t_D)}}{1-e^{-\gamma\tau}}\right) \tag{1.21}$$

1.2.3.2 Infusion

For infusion, the link between A B, and C, and the parameters (V, k, k_{12}, k_{21}, k_{13} and k_{31}), or (CL, V_1, Q_2, V_2, Q_3 and V_3) is defined as follows:

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

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

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

- single dose

$$C(t) = \begin{cases} \frac{D}{Tinf}\left[\begin{array}{l} \frac{A}{\alpha}\left(1-e^{-\alpha(t-t_D)}\right) \\ +\frac{B}{\beta}\left(1-e^{-\beta(t-t_D)}\right) \\ +\frac{C}{\gamma}\left(1-e^{-\gamma(t-t_D)}\right) \end{array}\right] & \text{if } t-t_D \leq Tinf, \\ \frac{D}{Tinf}\left[\begin{array}{l} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)} \\ +\frac{C}{\gamma}\left(1-e^{-\gamma Tinf}\right)e^{-\gamma(t-t_D-Tinf)} \end{array}\right] & \text{if not.} \end{cases} \tag{1.22}$$

- multiple doses

$$C(t) = \begin{cases} \sum_{i=1}^{n-1} \frac{D_i}{Tinf_i} \begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{C}{\gamma}\left(1-e^{-\gamma Tinf_i}\right)e^{-\gamma\left(t-t_{D_i}-Tinf_i\right)} \end{bmatrix} & \\ \quad + \frac{D}{Tinf_n} \begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha(t-t_{D_n})}\right) \\ +\frac{B}{\beta}\left(1-e^{-\beta(t-t_{D_n})}\right) \\ +\frac{C}{\gamma}\left(1-e^{-\gamma(t-t_{D_n})}\right) \end{bmatrix} & \text{if } t-t_{D_n} \leq Tinf, \\ \sum_{i=1}^{n} \frac{D_i}{Tinf_i} \begin{bmatrix} \frac{A}{\alpha}\left(1-e^{-\alpha Tinf_i}\right)e^{-\alpha\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{B}{\beta}\left(1-e^{-\beta Tinf_i}\right)e^{-\beta\left(t-t_{D_i}-Tinf_i\right)} \\ +\frac{C}{\gamma}\left(1-e^{-\gamma Tinf_i}\right)e^{-\gamma\left(t-t_{D_i}-Tinf_i\right)} \end{bmatrix} & \text{if not.} \end{cases} \tag{1.23}$$

- steady state

$$C(t) = \begin{cases} \frac{D}{Tinf} \begin{bmatrix} \frac{A}{\alpha}\left(\begin{array}{l}\left(1-e^{-\alpha(t-t_D)}\right) \\ +e^{-\alpha\tau}\frac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}}\end{array}\right) \\ +\frac{B}{\beta}\left(\begin{array}{l}\left(1-e^{-\beta(t-t_D)}\right) \\ +e^{-\beta\tau}\frac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}}\end{array}\right) \\ +\frac{C}{\gamma}\left(\begin{array}{l}\left(1-e^{-\gamma(t-t_D)}\right) \\ +e^{-\gamma\tau}\frac{\left(1-e^{-\gamma Tinf}\right)e^{-\gamma(t-t_D-Tinf)}}{1-e^{-\gamma\tau}}\end{array}\right) \end{bmatrix} & \text{if } t-t_D \leq Tinf, \\ \frac{D}{Tinf} \begin{bmatrix} \frac{A}{\alpha}\left(\frac{\left(1-e^{-\alpha Tinf}\right)e^{-\alpha(t-t_D-Tinf)}}{1-e^{-\alpha\tau}}\right) \\ +\frac{B}{\beta}\left(\frac{\left(1-e^{-\beta Tinf}\right)e^{-\beta(t-t_D-Tinf)}}{1-e^{-\beta\tau}}\right) \\ +\frac{C}{\gamma}\left(\frac{\left(1-e^{-\gamma Tinf}\right)e^{-\gamma(t-t_D-Tinf)}}{1-e^{-\gamma\tau}}\right) \end{bmatrix} & \text{if not.} \end{cases} \tag{1.24}$$

1.2.3.3 First order absorption

For first order absorption, the link between A B, and C, and the parameters (k_a, V, k, k_{12}, k_{21}, k_{13} and k_{31}), or (k_a, CL, V_1, Q_2, V_2, Q_3 and V_3) is defined as follows:

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

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

- single dose

$$C(t) = D\left(Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)} + Ce^{-\gamma(t-t_D)} - (A+B+C)e^{-k_a(t-t_D)}\right) \tag{1.25}$$

- multiple doses

$$C(t) = \sum_{i=1}^{n} D_i\left(Ae^{-\alpha\left(t-t_{D_i}\right)} + Be^{-\beta\left(t-t_{D_i}\right)} + Ce^{-\gamma\left(t-t_{D_i}\right)} - (A+B+C)e^{-k_a\left(t-t_{D_i}\right)}\right) \tag{1.26}$$

- steady state

$$C(t) = D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}} + \frac{Ce^{-\gamma(t-t_D)}}{1-e^{-\gamma\tau}} - \frac{(A+B+C)e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \tag{1.27}$$

NB: Equations 1.19 to 1.27 correspond to models n°13 to n°18 in Appendix I.1.

1.3 Models with Michaelis-Menten elimination

The list of PK models with Michaelis-Menten elimination implemented in PFIM are summarised in Appendix I.2. Presently, there is no implementation for multiple dosing with IV bolus administration in the PFIM software. For infusion and oral administration, the implementation in PFIM does not allow designs with different groups of doses as the dose is included in the model.

1.3.1 One-compartment models

1.3.1.1 Intravenous bolus

- single dose

$$\begin{aligned} &\text{Initial conditions: } \begin{cases} C(t) & = 0 \text{ for } t < t_D \\ C(t_D) & = \frac{D}{V} \end{cases} \\ &\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} \end{aligned} \tag{1.28}$$

1.3.1.2 Infusion

- single dose

$$\begin{aligned} &\text{Initial conditions: } C(t) = 0 \text{ for } t < t_D \\ &\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + input \\ &input(t) = \begin{cases} \frac{D}{Tinf}\frac{1}{V} & \text{if } 0 \le t - t_D \le Tinf \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.29}$$

- multiple doses

$$\begin{aligned}&\text{Initial conditions: } C(t) = 0 \text{ for } t < t_{D_1}\\ &\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + input\\ &input(t) = \begin{cases}\dfrac{D_i}{Tinf_i}\dfrac{1}{V} & \text{if } 0 \leq t - t_{D_i} \leq Tinf_i,\\ 0 & \text{if not.}\end{cases}\end{aligned} \tag{1.30}$$

1.3.1.3 First order absorption

- single dose

$$\begin{aligned}&\text{Initial conditions: } C(t) = 0 \text{ for } t < t_D\\ &\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + input\\ &input(t) = \frac{D}{V} k_a e^{-k_a(t - t_D)}\end{aligned} \tag{1.31}$$

- multiple doses

$$\begin{aligned}&\text{Initial conditions: } C(t) = 0 \text{ for } t < t_{D_1}\\ &\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + input\\ &input(t) = \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a\left(t - t_{D_i}\right)}\end{aligned} \tag{1.32}$$

NB: Equations 1.28 to 1.32 correspond to model n°1 to n°3 in Appendix I.2.

1.3.2 Two-compartment models

1.3.2.1 Intravenous bolus

- single dose

$$\begin{aligned}&\text{Initial conditions: } \begin{cases}C_1(t) = & 0 \text{ for } t < t_D\\ C_2(t) = & 0 \text{ for } t \leq t_D\\ C_1(t_D) = & \dfrac{D}{V}\end{cases}\\ &\frac{dC_1}{dt} = -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2\\ &\frac{dC_2}{dt} = \frac{k_{12}V}{V_2}C_1 - k_{21}C_2\end{aligned} \tag{1.33}$$

1.3.2.2 Infusion

- single dose

$$\begin{aligned}
&\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \end{cases} \\
&\frac{dC_1}{dt} = -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 + input \\
&\frac{dC_2}{dt} = \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\
&input(t) = \begin{cases} \frac{D}{Tinf}\frac{1}{V} & \text{if } 0 \leq t - t_D \leq Tinf \\ 0 & \text{if not.} \end{cases}
\end{aligned} \tag{1.34}$$

- multiple doses

$$\begin{aligned}
&\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_{D_1} \\ C_2(t) = & 0 \text{ for } t \leq t_{D_1} \end{cases} \\
&\frac{dC_1}{dt} = -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 + input \\
&\frac{dC_2}{dt} = \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\
&input(t) = \begin{cases} \frac{D_i}{Tinf_i}\frac{1}{V} & \text{if } 0 \leq t - t_{D_i} \leq Tinf_i, \\ 0 & \text{if not.} \end{cases}
\end{aligned} \tag{1.35}$$

1.3.2.3 First order absorption

- single dose

$$\begin{aligned}
&\text{Initial conditions: } \begin{cases} C_1(t) = & 0 \text{ for } t < t_D \\ C_2(t) = & 0 \text{ for } t \leq t_D \end{cases} \\
&\frac{dC_1}{dt} = -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 + input \\
&\frac{dC_2}{dt} = \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\
&input(t) = \frac{D}{V}k_a e^{-k_a(t-t_D)}
\end{aligned} \tag{1.36}$$

- multiple doses

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

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 + input \\ \frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\ input(t) &= \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a\left(t - t_{D_i}\right)} \end{aligned} \tag{1.37}$$

NB: Equations 1.33 to 1.37 correspond to models n°4 to n°9 in Appendix I.2.

1.3.3 Three-compartment models

1.3.3.1 Intravenous bolus

- single dose

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

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 \\ \frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= \frac{k_{13}V}{V_3}C_1 - k_{31}C_3 \end{aligned} \tag{1.38}$$

1.3.3.2 Infusion

- single dose

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

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 + input \\ \frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= \frac{k_{13}V}{V_3}C_1 - k_{31}C_3 \\ input(t) &= \begin{cases} \dfrac{D}{Tinf}\dfrac{1}{V} & \text{if } 0 \leq t - t_D \leq Tinf \\ 0 & \text{if not.} \end{cases} \end{aligned} \tag{1.39}$$

- multiple doses

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

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 + input \\ \frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= \frac{k_{13}V}{V_3}C_1 - k_{31}C_3 \end{aligned} \tag{1.40}$$

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

1.3.3.3 First order absorption

- single dose

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

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 + input \\ \frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= \frac{k_{13}V}{V_3}C_1 - k_{31}C_3 \end{aligned} \tag{1.41}$$

$$input(t) = \frac{D}{V}k_a e^{-k_a(t-t_D)}$$

- multiple doses

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

$$\begin{aligned} \frac{dC_1}{dt} &= -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 + input \\ \frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\ \frac{dC_3}{dt} &= \frac{k_{13}V}{V_3}C_1 - k_{31}C_3 \end{aligned} \tag{1.42}$$

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

NB: Equations 1.38 to 1.42 correspond to models n°10 to n°15 in Appendix I.2.

Chapter 2

Pharmacodynamic models

This chapter describes the pharmacodynamic models implemented in the PFIM software. Some of these pharmacodynamic models can be used alone or linked to a pharmacokinetic model. Some can only be used linked to any pharmacokinetic model. Two different types 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)

The list of the immediate response models implemented in PFIM is summarised in Appendix II.1 and II.2. The list of the turnover models is summarised in Appendix II.3.

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.

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 PFIM library.

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 (*i.e.* 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

$$S(t) = S_0e^{-k_{prog}t} \tag{2.12}$$

- 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 $S(t)$.

2.1.3 PFIM model function examples

Any combination of the 9 drug action models and 5 baseline/disease models is available in PFIM. 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°11: immed_Emax_const in Appendix II.1.

As a second example, the combination of an I_{max} model for the drug action (2.7) with a exponential progression as baseline/disease model (2.12) will give:

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

which corresponds to the model n°13: immed_Imax_exp in Appendix II.2.

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.

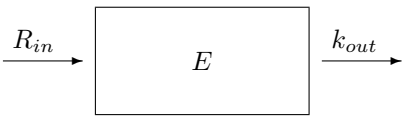

Figure 2.1: Turnover model of the effect E

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 $C(t) = 0$, $E(t) = \frac{R_{in}}{k_{out}}$.

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

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

- sigmoïd E_{max} model

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

- I_{max} model

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

- sigmoïd I_{max} model

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

- full I_{max} model

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

- sigmoïd full I_{max} model

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

NB: Equation 2.16 to 2.21 correspond to models n°1 to n°6 in Appendix II.3

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

- E_{max} model

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

- sigmoïd E_{max} model

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

- I_{max} model

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

- sigmoïd I_{max} model

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

- full I_{max} model

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

- sigmoïd full I_{max} model

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

NB: Equation 2.22 to 2.27 correspond to models n°7 to n°12 in Appendix II.3

Appendix

List and names of the PK and PD models available in PFIM (PFIM since version 3.2.1 and PFIM Interface since version 3.1)

Appendix I: list of models in PK library

For the use in the PFIM software, some variables are required (or not) for each PK model. They are specified in the column named Needed variables: N: the number of doses, tau: the interval between two doses, TInf: the duration of the infusion, doseMM: dose for models with Michaelis-Menten elimination (for models with linear elimination, dose is specified in the file stdin.r).

Appendix I.1: PK models with linear elimination

	Name	Input	Cpt	Parameterisation	Administration	Needed Variable(s)
1	**bolus_1cpt_Vk**	IV-bolus	1	V, k	sd	-
					md	N, tau
					ss	tau
2	**bolus_1cpt_VCl**	IV-bolus	1	V, Cl	sd	-
					md	N, tau
					ss	tau
3	**infusion_1cpt_Vk**	IV-infusion	1	V, k	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
4	**infusion_1cpt_VCl**	IV-infusion	1	V, Cl	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
5	**oral1_1cpt_kaVk**	1st order	1	ka, V, k	sd	-
					md	N, tau
					ss	tau
6	**oral1_1cpt_kaVCl**	1st order	1	ka, V, Cl	sd	-
					md	N, tau
					ss	tau
7	**bolus_2cpt_Vkk12k21**	IV-bolus	2	V, k, k12, k21	sd	-
					md	N, tau
					ss	tau
8	**bolus_2cpt_ClV1QV2**	IV-bolus	2	Cl, V1, Q, V2	sd	-
					md	N, tau
					ss	tau
9	**infusion_2cpt_Vkk12k21**	IV-infusion	2	V, k, k12, k21	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
10	**infusion_2cpt_ClV1QV2**	IV-infusion	2	Cl, V1, Q, V2	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau

	Name	Input	Cpt	Parameterisation	Administration	Needed Variable(s)
11	**oral1_2cpt_kaVkk12k21**	1st order	2	ka, V, k, k12, k21	sd	-
					md	N, tau
					ss	tau
12	**oral1_2cpt_kaClV1QV2**	1st order	2	ka, Cl, V1, Q, V2	sd	-
					md	N, tau
					ss	tau
13	**bolus_3cpt_Vkk12k21k13k31**	IV-bolus	3	V, k, k12, k21, k13, k31	sd	-
					md	N, tau
					ss	tau
14	**bolus_3cpt_ClV1Q1V2Q2V3**	IV-bolus	3	Cl, V1, Q1, V2, Q2, V3	sd	-
					md	N, tau
					ss	tau
15	**infusion_3cpt_Vkk12k21k13k31**	IV-infusion	3	V, k, k12, k21, k13, k31	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
16	**infusion_3cpt_ClV1Q1V2Q2V3**	IV-infusion	3	Cl, V1, Q1, V2, Q2, V3	sd	TInf
					md	TInf, N, tau
					ss	TInf, tau
17	**oral1_3cpt_kaVkk12k21k13k31**	1st order	3	ka, V, k, k12, k21, k13, k31	sd	-
					md	N, tau
					ss	tau
18	**oral1_3cpt_kaClV1Q1V2Q2V3**	1st order	3	ka, Cl, V1, Q1, V2, Q2, V3	sd	-
					md	N, tau
					ss	tau

Appendix I.2: PK models with Michaelis-Menten elimination

	Name	Input	Cpt	Parameterisation	Administration	Needed Variable(s)
1	**bolus_1cpt_VVmkm**	IV-bolus	1	V, Vm, km	sd	-
2	**infusion_1cpt_VVmkm**	IV-infusion	1	V, Vm, km	sd md	doseMM,TInf doseMM,TInf, tau
3	**oral1_1cpt_kaVVmkm**	1st order	1	ka, V,Vm, km	sd md	doseMM doseMM,tau
4	**bolus_2cpt_Vk12k21Vmkm**	IV-bolus	2	V, k12, k21, Vm, km	sd	-
5	**bolus_2cpt_V1QV2Vmkm**	IV-bolus	2	V1, Q, V2, Vm, km	sd	-
6	**infusion_2cpt_Vk12k21Vmkm**	IV-infusion	2	V, k12, k21, Vm, km	sd md	doseMM,TInf doseMM,TInf, tau
7	**infusion_2cpt_ V1QV2Vmkm**	IV-infusion	2	V1, Q, V2, Vm, km	sd md	doseMM,TInf doseMM,TInf, tau
8	**oral1_2cpt_kaVk12k21Vmkm**	1st order	2	ka, V, k12, k21, Vm, km	sd md	doseMM doseMM, tau
9	**oral1_2cpt_kaV1QV2Vmkm**	1st order	2	ka, V1, Q, V2, Vm, km	sd md	doseMM doseMM, tau
10	**bolus_3cpt_Vk12k21k31k13Vmkm**	IV-bolus	3	V, k12, k21, k13, k31, Vm, km	sd	-
11	**bolus_3cpt_ V1Q1V2Q2V3Vmkm**	IV-bolus	3	V1, Q1, V2, Q2, V3, Vm, km	sd	-
12	**infusion_3cpt_Vk12k21k13k31Vmkm**	IV-infusion	3	V, k12, k21, k13, k31, Vm, km	sd md	doseMM,TInf doseMM,TInf, tau
13	**infusion_3cpt_V1Q1V2Q2V3Vmkm**	IV-infusion	3	V1, Q1, V2, Q2, V3, Vm, km	sd md	doseMM,TInf doseMM,TInf, tau
14	**oral1_3cpt_kak12k21k13k31Vmkm**	1st order	3	ka, k12, k21, k13, k31, Vm, km	sd md	doseMM doseMM,tau
15	**oral1_3cpt_kaV1Q1V2Q2V3Vmkm**	1st order	3	ka, V1, Q1, V2, Q2, V3, Vm, km	sd md	doseMM doseMM, tau

Appendix II: list of models in PD library

The implementation of the PD models in the PFIM software differs if the PD model is used alone or linked to a pharmacokinetic model. The immediate response models used alone are described in Appendix II.1. The list of the immediate response PD models for PK/PD is thus given in Appendix II.1 plus those of Appendix II.2. Lastly, the list of turnover PD models for PK/PD is given in Appendix II.3.

For the case where a PK model with linear elimination is associated to a turnover PD response model, the PK model is written with a differential equations system. Consequently, only some PK models from Appendix I.1 are implemented:

- for IV bolus, only single dose models
- for infusion and oral absorption, single dose and multiple doses

Appendix II.1: Immediate response PD models for PD only

Drug action models	Baseline					
	Null baseline			Constant baseline		
		Name	Parameterisation		Name	Parameterisation
Linear	1	immed_lin_null	Alin	8	immed_lin_const	Alin, S0
Quadratic	2	immed_quad_null	Alin, Aquad	9	immed_quad_const	Alin, Aquad, S0
Logarithmic	3	immed_log_null	Alog	10	immed_log_const	Alog, S0
Emax	4	immed_Emax_null	Emax, C50	11	immed_Emax_const	Emax, C50, S0
Sigmoid Emax	5	immed_gammaEmax_null	Emax, C50, gamma	12	immed_gammaEmax_const	Emax, C50, gamma, S0
Imax	6	immed_Imax_null	Imax, C50	13	immed_Imax_const	Imax, C50, S0
Sigmoid Imax	7	immed_gammaImax_null	Imax, C50, gamma	14	immed_gammaImax_const	Imax, C50, gamma, S0

Appendix II.2: Immediate response PD models for PK/PD

Drug action models	Baseline/disease models									
	Linear progression			Exponential increase			Exponential decrease			
	Name		Param.	Name		Param.	Name		Param.
Linear	immed_lin_lin	1	Alin, S0, kprog	immed_lin_exp	8	Alin, S0, kprog	immed_lin_dexp	15	Alin, S0, kprog
Quadratic	immed_quad_lin	2	Alin, Aquad, S0, kprog	immed_quad_exp	9	Alin, Aquad, S0, kprog	immed_quad_dexp	16	Alin, Aquad, S0, kprog
Logarithmic	immed_log_lin	3	Alog, S0, kprog	immed_log_exp	10	Alog, S0, kprog	immed_log_dexp	17	Alog, S0, kprog
Emax	immed_Emax_lin	4	Emax, C50, S0, kprog	immed_Emax_exp	11	Emax, C50, S0, kprog	immed_Emax_dexp	18	Emax, C50, S0, kprog
Sigmoid Emax	immed_gammaEmax_lin	5	Emax, C50, gamma, S0, kprog	immed_gammaEmax_exp	12	Emax, C50, gamma, S0, kprog	immed_gammaEmax_dexp	19	Emax, C50, gamma, S0, kprog
Imax	immed_Imax_lin	6	Imax, C50, S0, kprog	immed_Imax_exp	13	Imax, C50, S0, kprog	immed_Imax_dexp	20	Imax, C50, S0, kprog
Sigmoid Imax	immed_gammaImax_lin	7	Imax, C50, gamma, S0, kprog	immed_gammaImax_exp	14	Imax, C50, gamma, S0, kprog	immed_gammaImax_dexp	21	Imax, C50, gamma, S0, kprog

Appendix II.3: Turnover PD models for PK/PD

Types of response	Models with impact on the					
	Input			Output		
		Name	Parameterisation		Name	Parameterisation
Emax	1	turn_input_Emax	Rin,kout,Emax,C50	7	turn_output_Emax	Rin,kout,Emax,C50
Sigmoid Emax	2	turn_input_gammaEmax	Rin,kout,Emax,C50,gamma	8	turn_output_gammaEmax	Rin,kout,Emax,C50,gamma
Imax	3	turn_input_Imax	Rin,kout,Imax,C50	9	turn_output_Imax	Rin,kout,Imax,C50
Sigmoid Imax	4	turn_input_gammaImax	Rin,kout,Imax,C50,gamma	10	turn_output_gammaImax	Rin,kout,Imax,C50,gamma
Full Imax	5	turn_input_Imaxfull	Rin,kout,C50	11	turn_output_Imaxfull	Rin,kout,C50
Sigmoid full Imax	6	turn_input_gammaImaxfull	Rin,kout,C50,gamma	12	turn_output_gammaImaxfull	Rin,kout,C50,gamma