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

Anne Dubois, Julie Bertrand and France Mentré
UMR738, INSERM, University Paris Diderot

Programmer: Anne Dubois

March 2011
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

1 Pharmacokinetic models .................................................. 5
  1.1 Compartmental models and parameters ................................. 6
    1.1.1 One-compartment models ........................................ 6
    1.1.2 Two-compartment models ........................................ 7
    1.1.3 Three-compartment models ...................................... 7
  1.2 Models with linear elimination ...................................... 9
    1.2.1 One-compartment models ........................................ 9
      1.2.1.1 Intravenous bolus ........................................ 9
      1.2.1.2 Infusion ............................................... 9
      1.2.1.3 First order absorption ................................ 10
    1.2.2 Two-compartment models ....................................... 10
      1.2.2.1 Intravenous bolus ........................................ 11
      1.2.2.2 Infusion ............................................... 11
      1.2.2.3 First order absorption ................................ 12
    1.2.3 Three-compartment models ..................................... 13
      1.2.3.1 Intravenous bolus ........................................ 14
      1.2.3.2 Infusion ............................................... 14
      1.2.3.3 First order absorption ................................ 16
  1.3 Models with Michaelis-Menten elimination .......................... 17
    1.3.1 One-compartment models ........................................ 17
      1.3.1.1 Intravenous bolus ........................................ 17
      1.3.1.2 Infusion ............................................... 17
      1.3.1.3 First order absorption ................................ 18
    1.3.2 Two-compartment models ....................................... 19
      1.3.2.1 Intravenous bolus ........................................ 19
      1.3.2.2 Infusion ............................................... 19
      1.3.2.3 First order absorption ................................ 20
    1.3.3 Three-compartment models ..................................... 21
      1.3.3.1 Intravenous bolus ........................................ 21
      1.3.3.2 Infusion ............................................... 21
      1.3.3.3 First order absorption ................................ 22

2 Pharmacodynamic models ................................................. 24
  2.1 Immediate response models ......................................... 24
    2.1.1 Drug action models ........................................... 25
2.1.2 Baseline/disease models ........................................... 26
2.1.3 PFIM model function examples .................................. 26
2.2 Turnover response models ........................................... 27
  2.2.1 Models with impact on the input (\( R_{in} \)) .................. 27
  2.2.2 Models with impact on the output (\( k_{out} \)) ............... 28

Appendix ......................................................... 29
  Appendix I: list of models in PK library ........................... 29
    Appendix I.1: PK models with linear elimination ................ 30
    Appendix I.1: PK models with Michaelis-Menten elimination .... 32
  Appendix II: list of models in PD library .......................... 33
    Appendix II.1: Immediate response PD models for PD only ...... 34
    Appendix II.2: Immediate response PD models for PK/PD ........ 35
    Appendix II.3: Turnover PD models for PK/PD ................. 36
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 $D_i$ ($i = 1, \ldots, n$) 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 $\tau$ ($t \geq t_D$)
1.1. COMPARTMENTAL MODELS AND PARAMETERS

For infusion, the duration of infusion is $T_{inf}$ for single dose and $T_{inf_i}$ ($i = 1, ... n$) 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 $t_{D_i+1} - t_{D_i} > T_{inf_i}$ for infusion).

For steady state, the interval $\tau$ is supposed to be greater than infusion duration ($\tau > T_{inf}$).

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: $V_m$ is in amount 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).](image)

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 $k = \frac{CL}{V}$. 

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

\[
\begin{align*}
V &= V_1 \\
&\quad \xrightarrow{k_{12}} \quad V_2 \\
&\quad \xrightarrow{k_{21}} \quad (\text{a})
\end{align*}
\]

\[
\begin{align*}
V_1 &\quad \xrightarrow{Q} \quad V_2 \\
&\quad \xrightarrow{CL} \quad (\text{b})
\end{align*}
\]

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: \((V, k, k_{12} \text{ and } k_{21})\), or \((CL, V_1, Q \text{ and } V_2)\). For extra-vascular administration, \( V_1 (V) \), \( V_2 \), \( CL \), and \( Q \) are apparent volumes and clearances.

The second parameterisation terms are derived using:

- \( V_1 = V \)
- \( CL = k \times V_1 \)
- \( Q = k_{12} \times V_1 \)
- \( V_2 = \frac{k_{12}}{k_{21}} \times V_1 \)

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.
1.1. COMPARTMENTAL MODELS AND PARAMETERS

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: \((V, k, k_{12}, k_{21}, k_{13} \text{ and } k_{31})\), or \((CL, V_1, Q_2, V_2, Q_3 \text{ and } V_3)\). 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

\[
C(t) = \frac{D}{V} e^{-k(t-t_D)}
\]  

(1.1)

- multiple doses

\[
C(t) = \sum_{i=1}^{n} \frac{D_i}{V} e^{-k(t-t_{D_i})}
\]  

(1.2)

- steady state

\[
C(t) = \frac{D e^{-k(t-t_D)}}{V} \left(1 - e^{-k\tau}\right)
\]  

(1.3)

1.2.1.2 Infusion

- single dose

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

(1.4)

- multiple doses

\[
C(t) = \begin{cases} 
\sum_{i=1}^{n-1} \frac{D_i}{Tinf_i} \frac{1}{kV} (1 - e^{-kTinf_i}) e^{-k(t-t_{D_i}-Tinf_i)} & \text{if } t - t_{D_n} \leq Tinf_n, \\
\frac{D_n}{Tinf_n} \frac{1}{kV} (1 - e^{-k(t-t_{D_n})}) & \\
\sum_{i=1}^{n} \frac{D_i}{Tinf_i} \frac{1}{kV} (1 - e^{-kTinf_i}) e^{-k(t-t_{D_i}-Tinf_i)} & \text{if not.}
\end{cases}
\]  

(1.5)
1.2. MODELS WITH LINEAR ELIMINATION

- steady state

\[
C(t) = \begin{cases} 
\frac{D}{T_{inj} k V} \left( \frac{1 - e^{-k(t-t_D)}}{1 - e^{-k\tau}} \right) & \text{if } (t - t_D) \leq T_{inj}, \\
\frac{D}{T_{inj} k V} \frac{1 - e^{-k(t-t_D)}}{1 - e^{-k\tau}} & \text{if not.}
\end{cases}
\]

\[
(1.6)
\]

1.2.1.3 First order absorption

- single dose

\[
C(t) = \frac{D}{V} \frac{k_a}{k - k_a} \left( e^{-k(t-t_D)} - e^{-k_a(t-t_D)} \right)
\]

\[
(1.7)
\]

- multiple doses

\[
C(t) = \sum_{i=1}^{n} \frac{D_i}{V} \frac{k_a}{k - k_a} \left( e^{-k(t-t_{Di})} - e^{-k_a(t-t_{Di})} \right)
\]

\[
(1.8)
\]

- steady state

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

\[
(1.9)
\]

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 \( \alpha, \beta, A \) and \( B \) defined by the following expressions:

\[- \alpha = \frac{k_{21} k}{\beta} = \frac{Q \cdot CL}{V_2 \cdot V_1} \]

\[- \beta = \frac{1}{2} \left[ \frac{1}{2} \left( \frac{Q}{V_1} + \frac{Q}{V_2} + \frac{CL}{V_1} \right)^2 - 4 \frac{Q \cdot CL}{V_2 \cdot V_1} \right] \]

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. MODELS WITH LINEAR ELIMINATION

1.2.2.1 Intravenous bolus

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

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

• single dose

\[
C(t) = D \left( A e^{-\alpha(t-t_D)} + B e^{-\beta(t-t_D)} \right)
\]  

(1.10)

• multiple doses

\[
C(t) = \sum_{i=1}^{n} D_i \left( A e^{-\alpha(t-t_{D_i})} + B e^{-\beta(t-t_{D_i})} \right)
\]  

(1.11)

• steady state

\[
C(t) = D \left( \frac{A e^{-\alpha t}}{1 - e^{-\alpha t}} + \frac{B e^{-\beta t}}{1 - e^{-\beta t}} \right)
\]  

(1.12)

1.2.2.2 Infusion

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

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

• single dose

\[
C(t) = \begin{cases} 
\frac{D}{T_{inf}} \left[ \frac{A}{\alpha} (1 - e^{-\alpha(t-t_D)}) \right] \\
\frac{D}{T_{inf}} \left[ \frac{B}{\beta} (1 - e^{-\beta(t-t_D)}) \right]
\end{cases}
\]  

if \(t - t_D \leq T_{inf}\),

\[
C(t) = \begin{cases} 
\frac{D}{T_{inf}} \left[ \frac{A}{\alpha} (1 - e^{-\alpha t}) e^{-\alpha(t-t_{D-Tinf})} \right] \\
\frac{D}{T_{inf}} \left[ \frac{B}{\beta} (1 - e^{-\beta t}) e^{-\beta(t-t_{D-Tinf})} \right]
\end{cases}
\]  

if not.

(1.13)
1.2. MODELS WITH LINEAR ELIMINATION

- multiple doses

\[
C(t) = \begin{cases}
\sum_{i=1}^{n-1} \frac{D_i}{Tinf_i} \left[ \frac{A}{\alpha} \left(1 - e^{-\alpha Tinf_i}\right) e^{-\alpha(t-t_{D_i}-Tinf_i)} \right] \\
\sum_{i=1}^{n} \frac{D_i}{Tinf_i} \left[ \frac{A}{\alpha} \left(1 - e^{-\alpha(t-t_{D_i})}\right) \right] + \frac{D}{Tinf} \left[ \frac{A}{\alpha} \left(1 - e^{-\alpha(t-t_{D_n})}\right) \right]
\end{cases}
\]

if \( t - t_{D_n} \leq Tinf \),

\[
\frac{A}{\alpha} \left(1 - e^{-\alpha(t-t_{D_n})}\right) e^{-\alpha(t-t_{D_n}-Tinf)} + \frac{B}{\beta} \left(1 - e^{-\beta(t-t_{D_n})}\right)
\]

if not.

- steady state

\[
C(t) = \begin{cases}
\frac{D}{Tinf} \left[ \frac{A}{\alpha} \left(1 - e^{-\alpha(t-t_{D})}\right) \right] + \frac{B}{\beta} \left(1 - e^{-\beta(t-t_{D})}\right)
\end{cases}
\]

if \( t - t_{D} \leq Tinf \),

\[
\frac{A}{\alpha} \left(1 - e^{-\alpha(t-t_{D})}\right) e^{-\alpha(t-t_{D}-Tinf)} + \frac{B}{\beta} \left(1 - e^{-\beta(t-t_{D}-Tinf)}\right)
\]

if not.

1.2.2.3 First order absorption

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

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

\[
- \ B = \frac{k_a}{V} \frac{k_{21} - \beta}{(k_a - \beta)(\alpha - \beta)} = \frac{k_a}{V_1} \frac{Q}{\frac{V_2 - \beta}{(k_a - \beta)(\alpha - \beta)}}
\]
1.2. MODELS WITH LINEAR ELIMINATION

- **single dose**
  \[
  C(t) = D \left( Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)} - (A + B)e^{-ka(t-t_D)} \right)
  \]  
  (1.16)

- **multiple doses**
  \[
  C(t) = \sum_{i=1}^{n} D_i \left( Ae^{-\alpha(t-t_{D_i})} + Be^{-\beta(t-t_{D_i})} - (A + B)e^{-ka(t-t_{D_i})} \right)
  \]  
  (1.17)

- **steady state**
  \[
  C(t) = D \left( \frac{Ae^{-\alpha(t-t_D)}}{1 - e^{-\alpha \tau}} + \frac{Be^{-\beta(t-t_D)}}{1 - e^{-\beta \tau}} - \frac{(A + B)e^{-ka(t-t_D)}}{1 - e^{-ka \tau}} \right)
  \]  
  (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 \(\alpha\), \(\beta\), \(\gamma\), \(A\), \(B\) and \(C\) defined by the following expressions:

- \(a_0 = kk_{21}k_{31} = \frac{CLQ_2Q_3}{V_1V_2V_3}\)
- \(a_1 = \begin{cases} kk_{31} + k_{21}k_{31} + k_{21}k_{13} + kk_{21} + k_{31}k_{12} \\ CLQ_3 + \frac{Q_2Q_3}{V_2V_3} + \frac{Q_2Q_3}{V_1V_2} + \frac{CLQ_2}{V_1V_2} + \frac{Q_3Q_2}{V_3V_1} \end{cases}\)
- \(a_2 = \begin{cases} k + k_{12} + k_{13} + k_{21} + k_{31} \\ \frac{CL}{V_1} + \frac{Q_2}{V_1} + \frac{Q_3}{V_2} + \frac{Q_2}{V_3} + \frac{Q_3}{V_3} \end{cases}\)
- \(p = a_1 - a_2^2/3\)
- \(q = 2a_2^3/27 - a_1a_2/3 + a_0\)
- \(r_1 = \sqrt{-\left(\frac{p^3}{27}\right)}\)
- \(r_2 = 2r_1^{1/3}\)
- \(\phi = \arccos\left(-\frac{q}{2r_1}\right)/3\)
- \(\alpha = -\left(\cos(\phi) r_2 - a_2/3\right)\)
- \(\beta = -\left(\cos\left(\phi + \frac{2\pi}{3}\right) r_2 - a_2/3\right)\)
1.2. MODELS WITH LINEAR ELIMINATION

- $\gamma = - \left( \cos \left( \phi + \frac{4\pi}{3} \right) r_2 - a_2/3 \right)$

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:

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

- single dose
  
  $C(t) = D \left( Ae^{-\alpha(t-t_D)} + Be^{-\beta(t-t_D)} + Ce^{-\gamma(t-t_D)} \right)$  \hspace{1cm} (1.19)

- multiple doses
  
  $C(t) = \sum_{i=1}^{n} D_i \left( Ae^{-\alpha(t-t_{D_i})} + Be^{-\beta(t-t_{D_i})} + Ce^{-\gamma(t-t_{D_i})} \right)$  \hspace{1cm} (1.20)

- steady state
  
  $C(t) = D \left( \frac{Ae^{-\alpha(t-t_D)}}{1 - e^{-\alpha \tau}} + \frac{Be^{-\beta(t-t_D)}}{1 - e^{-\beta \tau}} + \frac{Ce^{-\gamma(t-t_D)}}{1 - e^{-\gamma \tau}} \right)$  \hspace{1cm} (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:

- $A = \frac{1}{V} \frac{k_{21} - \alpha k_{31} - \alpha}{\alpha - \beta} \frac{1}{\alpha - \gamma} = \frac{1}{V} \frac{Q_2}{\alpha - \beta} \frac{Q_3 - \alpha}{\alpha - \gamma}$
- $B = \frac{1}{V} \frac{k_{21} - \beta k_{31} - \beta}{\beta - \alpha} \frac{1}{\beta - \gamma} = \frac{1}{V} \frac{Q_2}{\beta - \alpha} \frac{Q_3 - \beta}{\beta - \gamma}$
1.2. MODELS WITH LINEAR ELIMINATION

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

- single dose

\[
C(t) = \begin{cases} \\
\frac{D}{T_{in}} \left[ \frac{A}{\alpha} (1 - e^{-\alpha(t-t_d)}) \right] + \frac{B}{\beta} (1 - e^{-\beta(t-t_d)}) \right] + \frac{C}{\gamma} (1 - e^{-\gamma(t-t_d)}) \right] & \text{if } t - t_d \leq T_{in} \\
\text{if not.} \end{cases}
\]

(1.22)

- multiple doses

\[
C(t) = \begin{cases} \\
\sum_{i=1}^{n-1} D_i \left[ \frac{A}{\alpha} (1 - e^{-\alpha(t-t_{D_i})}) \right] e^{-\alpha(t-t_{D_i}-T_{inf})} + \frac{B}{\beta} (1 - e^{-\beta(t-t_{D_i})}) e^{-\beta(t-t_{D_i}-T_{inf})} + \frac{C}{\gamma} (1 - e^{-\gamma(t-t_{D_i})}) e^{-\gamma(t-t_{D_i}-T_{inf})} \right] & \text{if } t - t_{D_n} \leq T_{in} \\
\sum_{i=1}^{n} D_i \left[ \frac{A}{\alpha} (1 - e^{-\alpha(t-t_{D_i})}) \right] e^{-\alpha(t-t_{D_i}-T_{inf})} + \frac{B}{\beta} (1 - e^{-\beta(t-t_{D_i})}) e^{-\beta(t-t_{D_i}-T_{inf})} + \frac{C}{\gamma} (1 - e^{-\gamma(t-t_{D_i})}) e^{-\gamma(t-t_{D_i}-T_{inf})} \right] & \text{if not.} \end{cases}
\]

(1.23)
1.2. MODELS WITH LINEAR ELIMINATION

- steady state

\[
C (t) = \begin{cases} \\
\frac{D}{T_{inf}} \left[ \frac{A}{\alpha} \left( \frac{1 - e^{-\alpha(t-t_{D})}}{1 - e^{-\alpha \tau}} \right) + B \left( \frac{1 - e^{-\beta(t-t_{D})}}{1 - e^{-\beta \tau}} \right) + C \left( \frac{1 - e^{-\gamma(t-t_{D})}}{1 - e^{-\gamma \tau}} \right) \right] & \text{if } t - t_{D} \leq T_{inf}, \\
\frac{D}{T_{inf}} \left[ \frac{A}{\alpha} \left( \frac{1 - e^{-\alpha T_{inf}}}{1 - e^{-\alpha \tau}} \right) + B \left( \frac{1 - e^{-\beta T_{inf}}}{1 - e^{-\beta \tau}} \right) + C \left( \frac{1 - e^{-\gamma T_{inf}}}{1 - e^{-\gamma \tau}} \right) \right] & \text{if not.}
\end{cases}
\]

(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:

- \( A = \frac{1}{V} \frac{k_{a} k_{21} - \alpha k_{31} - \alpha}{\alpha - \beta \alpha - \gamma} = \frac{1}{V_{1}} \frac{k_{a} Q_{2}}{V_{2}} - \frac{\alpha Q_{3}}{V_{3}} - \alpha \)

- \( B = \frac{1}{V} \frac{k_{a} k_{21} - \beta k_{31} - \beta}{\beta - \alpha \beta - \gamma} = \frac{1}{V_{1}} \frac{k_{a} Q_{2}}{V_{2}} - \frac{\beta Q_{3}}{V_{3}} - \beta \)

- \( C = \frac{1}{V} \frac{k_{a} k_{21} - \gamma k_{31} - \gamma}{\gamma - \beta \gamma - \alpha} = \frac{1}{V_{1}} \frac{k_{a} Q_{2}}{V_{2}} - \frac{\gamma Q_{3}}{V_{3}} - \gamma \)

- single dose

\[
C (t) = D \left( A e^{-\alpha(t-t_{D})} + B e^{-\beta(t-t_{D})} + C e^{-\gamma(t-t_{D})} \right) - (A + B + C) e^{-k_{a}(t-t_{D})}
\]

(1.25)

- multiple doses

\[
C (t) = \sum_{i=1}^{n} D_{i} \left( A e^{-\alpha(t-t_{D_{i}})} + B e^{-\beta(t-t_{D_{i}})} + C e^{-\gamma(t-t_{D_{i}})} \right) - (A + B + C) e^{-k_{a}(t-t_{D_{i}})}
\]

(1.26)
1.3 MODELS WITH MICHAELIS-MENTEN ELIMINATION

• steady state

\[ C(t) = D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}} + \frac{Ce^{-\gamma(t-t_D)}}{1-e^{-\gamma\tau}} - \frac{(A + B + C)e^{-ka(t-t_D)}}{1-e^{-ka\tau}}\right) \]  (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

Initial conditions:

\[
\begin{align*}
C(t) &= 0 \text{ for } t < t_D \\
C(t_D) &= \frac{D}{V}
\end{align*}
\]

\[
\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C}
\]  (1.28)

1.3.1.2 Infusion

• single dose

Initial conditions: \( C(t) = 0 \) for \( t < t_D \)

\[
\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + \text{input}
\]

\[
\text{input}(t) = \begin{cases} 
\frac{D}{Tinf} \frac{1}{V} & \text{if } 0 \leq t - t_D \leq Tinf \\
0 & \text{if not.}
\end{cases}
\]  (1.29)
1.3. MODELS WITH MICHAELIS-MENTEN ELIMINATION

- multiple doses

Initial conditions: \( C(t) = 0 \) for \( t < t_{D_1} \)

\[
\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + \text{input}
\]  

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

(1.30)

1.3.1.3 First order absorption

- single dose

Initial conditions: \( C(t) = 0 \) for \( t < t_D \)

\[
\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + \text{input}
\]  

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

(1.31)

- multiple doses

Initial conditions: \( C(t) = 0 \) for \( t < t_{D_1} \)

\[
\frac{dC}{dt} = -\frac{V_m \times C}{K_m + C} + \text{input}
\]  

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

(1.32)

NB: Equations 1.28 to 1.32 correspond to model n°1 to n°3 in Appendix I.2.
1.3. MODELS WITH MICHAELIS-MENTEN ELIMINATION

1.3.2 Two-compartment models

1.3.2.1 Intravenous bolus

- single dose

Initial conditions:
\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_D \\
C_2(t) &= 0 \text{ for } t \leq t_D \\
C_1(t_D) &= \frac{D}{V}
\end{align*}
\]

\[
\frac{dC_1}{dt} = -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2
\]

\[
\frac{dC_2}{dt} = \frac{k_{12}V}{V_2}C_1 - k_{21}C_2
\]

1.3.2.2 Infusion

- single dose

Initial conditions:
\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_D \\
C_2(t) &= 0 \text{ for } t \leq t_D
\end{align*}
\]

\[
\frac{dC_1}{dt} = -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 + \text{input}
\]

\[
\frac{dC_2}{dt} = \frac{k_{12}V}{V_2}C_1 - k_{21}C_2
\]

\[
\text{input}(t) = \begin{cases} 
\frac{D}{T_{inf}V} & \text{if } 0 \leq t - t_D \leq T_{inf} \\
0 & \text{if not.}
\end{cases}
\]

- multiple doses

Initial conditions:
\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_{D_i} \\
C_2(t) &= 0 \text{ for } t \leq t_{D_i}
\end{align*}
\]

\[
\frac{dC_1}{dt} = -\frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 + \text{input}
\]

\[
\frac{dC_2}{dt} = \frac{k_{12}V}{V_2}C_1 - k_{21}C_2
\]

\[
\text{input}(t) = \begin{cases} 
\frac{D_i}{T_{inf_i}V} & \text{if } 0 \leq t - t_{D_i} \leq T_{inf_i}, \\
0 & \text{if not.}
\end{cases}
\]
1.3. MODELS WITH MICHAELIS-MENTEN ELIMINATION

1.3.2.3 First order absorption

- single dose

Initial conditions: \[ \begin{align*} C_1 (t) &= 0 \text{ for } t < t_D \\
C_2 (t) &= 0 \text{ for } t \leq t_D \end{align*} \]

\[
\frac{dC_1}{dt} = \frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V} C_2 + \text{input} \tag{1.36}
\]

\[
\frac{dC_2}{dt} = \frac{k_{12}V}{V_2} C_1 - k_{21}C_2
\]

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

- multiple doses

Initial conditions: \[ \begin{align*} C_1 (t) &= 0 \text{ for } t < t_{D_1} \\
C_2 (t) &= 0 \text{ for } t \leq t_{D_1} \end{align*} \]

\[
\frac{dC_1}{dt} = \frac{V_m \times C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V} C_2 + \text{input} \tag{1.37}
\]

\[
\frac{dC_2}{dt} = \frac{k_{12}V}{V_2} C_1 - k_{21}C_2
\]

\[\text{input} (t) = \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a(t-t_{D_i})}\]

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

Initial conditions:
\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_D \\
C_2(t) &= 0 \text{ for } t \leq t_D \\
C_3(t) &= 0 \text{ for } t \leq t_D \\
C_1(t_D) &= \frac{D}{V}
\end{align*}
\]

\[
\begin{align*}
\frac{dC_1}{dt} &= - \frac{V_m}{V} \frac{C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 \\
\frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\
\frac{dC_3}{dt} &= \frac{k_{13}V}{V_3}C_1 - k_{31}C_3
\end{align*}
\] (1.38)

1.3.3.2 Infusion

- single dose

Initial conditions:
\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_D \\
C_2(t) &= 0 \text{ for } t \leq t_D \\
C_3(t) &= 0 \text{ for } t \leq t_D
\end{align*}
\]

\[
\begin{align*}
\frac{dC_1}{dt} &= - \frac{V_m}{V} \frac{C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 + \text{input} \\
\frac{dC_2}{dt} &= \frac{k_{12}V}{V_2}C_1 - k_{21}C_2 \\
\frac{dC_3}{dt} &= \frac{k_{13}V}{V_3}C_1 - k_{31}C_3
\end{align*}
\] (1.39)

\[
\text{input}(t) = \begin{cases} 
\frac{D}{Tinf} \frac{1}{V} & \text{if } 0 \leq t - t_D \leq Tinf \\
0 & \text{if not.}
\end{cases}
\]
1.3. MODELS WITH MICHAELIS-MENTEN ELIMINATION

- multiple doses

Initial conditions:
\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_{D_1} \\
C_2(t) &= 0 \text{ for } t \leq t_{D_1} \\
C_3(t) &= 0 \text{ for } t \leq t_{D_1}
\end{align*}
\]

\[
\frac{dC_1}{dt} = -\frac{V_m}{V} \frac{C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V} C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V} C_3 + \text{input}
\]

\[
\frac{dC_2}{dt} = k_{12}V C_1 - k_{21}C_2
\]

\[
\frac{dC_3}{dt} = k_{13}V C_1 - k_{31}C_3
\]

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

1.3.3.3 First order absorption

- single dose

Initial conditions:
\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_D \\
C_2(t) &= 0 \text{ for } t \leq t_D \\
C_3(t) &= 0 \text{ for } t \leq t_D
\end{align*}
\]

\[
\frac{dC_1}{dt} = -\frac{V_m}{V} \frac{C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V} C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V} C_3 + \text{input}
\]

\[
\frac{dC_2}{dt} = k_{12}V C_1 - k_{21}C_2
\]

\[
\frac{dC_3}{dt} = k_{13}V C_1 - k_{31}C_3
\]

\[
\text{input}(t) = \frac{D}{V} k_a e^{-k_a(t-t_D)}
\]
1.3. MODELS WITH MICHAELIS-MENTEN ELIMINATION

- multiple doses

Initial conditions:

\[
\begin{align*}
C_1(t) &= 0 \text{ for } t < t_{D_1} \\
C_2(t) &= 0 \text{ for } t \leq t_{D_1} \\
C_3(t) &= 0 \text{ for } t \leq t_{D_1}
\end{align*}
\]

\[
\begin{align*}
\frac{dC_1}{dt} &= -\frac{V_m}{V} \times \frac{C_1}{K_m + C_1} - k_{12}C_1 + \frac{k_{21}V_2}{V}C_2 - k_{13}C_1 + \frac{k_{31}V_3}{V}C_3 + \text{input} \\
\frac{dC_2}{dt} &= k_{12}V_2 C_1 - k_{21}C_2 \\
\frac{dC_3}{dt} &= k_{13}V_3 C_1 - k_{31}C_3 \\
\text{input}(t) &= \sum_{i=1}^{n} \frac{D_i}{V} k_a e^{-k_a(t-t_{D_i})}
\end{align*}
\]

**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:

$$E(t) = A(t) + S(t)$$  \hfill (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

- $A_{\text{lin}}$: constant associated to $C(t)$
- $A_{\text{quad}}$: constant associated to the square of $C(t)$
- $A_{\text{log}}$: constant associated to the logarithm of $C(t)$
- $E_{\text{max}}$: maximal agonistic response
- $I_{\text{max}}$: maximal antagonistic response
• $C_{50}$: concentration to get half of the maximal response (i.e. drug potency)
• $\gamma$: 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**
  \[ A(t) = A_{\text{lin}}C(t) \]  
  \[ (2.2) \]

- **quadratic model**
  \[ A(t) = A_{\text{lin}}C(t) + A_{\text{quad}}C(t)^2 \]  
  \[ (2.3) \]

- **logarithmic model**
  \[ A(t) = A_{\log\log}(C(t)) \]  
  \[ (2.4) \]

- **$E_{\text{max}}$ model**
  \[ A(t) = \frac{E_{\text{max}}C(t)}{C(t) + C_{50}} \]  
  \[ (2.5) \]

- **sigmoid $E_{\text{max}}$ model**
  \[ A(t) = \frac{E_{\text{max}}C(t)^\gamma}{C(t)^\gamma + C_{50}^\gamma} \]  
  \[ (2.6) \]

- **$I_{\text{max}}$ model**
  \[ A(t) = 1 - \frac{I_{\text{max}}C(t)}{C(t) + C_{50}} \]  
  \[ (2.7) \]

- **sigmoid $I_{\text{max}}$ model**
  \[ A(t) = 1 - \frac{I_{\text{max}}C(t)^\gamma}{C(t)^\gamma + C_{50}^\gamma} \]  
  \[ (2.8) \]
2.1. IMMEDIATE RESPONSE MODELS

2.1.2 Baseline/disease models

- null baseline
  \[ S(t) = 0 \] (2.9)

- constant baseline with no disease progression
  \[ S(t) = S_0 \] (2.10)

- linear disease progression
  \[ S(t) = S_0 + k_{\text{prog}} t \] (2.11)

- exponential disease increase
  \[ S(t) = S_0 e^{-k_{\text{prog}} t} \] (2.12)

- exponential disease decrease
  \[ S(t) = S_0 (1 - e^{-k_{\text{prog}} t}) \] (2.13)

**NB:** Only, for the \( I_{\text{max}} \) 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 \( E_{\text{max}} \) model for the drug action (2.5) and a constant baseline with no disease progression model (2.10) will result in the following equation:

\[ E(t) = S_0 + \frac{E_{\text{max}} C(t)}{C(t) + C_{50}} \] (2.14)

which corresponds to the model \( \text{n}^{\circ}11: \text{immed}_E\text{max}_E\text{const} \) in Appendix II.1.

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

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

which corresponds to the model \( \text{n}^{\circ}13: \text{immed}_I\text{max}_E\text{exp} \) 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 \( E \)](image)

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)
- \( \gamma \): 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

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

(2.16)

- sigmoid \( E_{max} \) model

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

(2.17)

- \( I_{max} \) model

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

(2.18)
2.2. TURNOVER RESPONSE MODELS

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

- full $I_{max}$ model
  \[
  \frac{dE}{dt} = R_{in} \left( 1 - \frac{C}{C + C_{50}} \right) - k_{out}E
  \]  
  (2.20)

- sigmoid full $I_{max}$ model
  \[
  \frac{dE}{dt} = R_{in} \left( 1 - \frac{C\gamma}{C\gamma + C_{50}} \right) - k_{out}E
  \]  
  (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
  \[
  \frac{dE}{dt} = R_{in} - k_{out} \left( 1 + \frac{E_{max}C}{C + C_{50}} \right) E
  \]  
  (2.22)

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

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

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

- full $I_{max}$ model
  \[
  \frac{dE}{dt} = R_{in} - k_{out} \left( 1 - \frac{C}{C + C_{50}} \right) E
  \]  
  (2.26)

- sigmoid full $I_{max}$ model
  \[
  \frac{dE}{dt} = R_{in} - k_{out} \left( 1 - \frac{C\gamma}{C\gamma + C_{50}} \right) E
  \]  
  (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, $T_{\text{Inf}}$: 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

<table>
<thead>
<tr>
<th>Name</th>
<th>Input</th>
<th>Cpt</th>
<th>Parameterisation</th>
<th>Administration</th>
<th>Needed Variable(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 bolus_1cpt_Vk</td>
<td>IV-bolus</td>
<td>1</td>
<td>V, k</td>
<td>sd, md, ss</td>
<td>- N, tau</td>
</tr>
<tr>
<td>2 bolus_1cpt_VCl</td>
<td>IV-bolus</td>
<td>1</td>
<td>V, Cl</td>
<td>sd, md, ss</td>
<td>- N, tau</td>
</tr>
<tr>
<td>3 infusion_1cpt_Vk</td>
<td>IV-infusion</td>
<td>1</td>
<td>V, k</td>
<td>sd</td>
<td>TInf, tau</td>
</tr>
<tr>
<td>4 infusion_1cpt_VCl</td>
<td>IV-infusion</td>
<td>1</td>
<td>V, Cl</td>
<td>sd</td>
<td>TInf, N, tau</td>
</tr>
<tr>
<td>5 orall_1cpt_kavk</td>
<td>1st order</td>
<td>1</td>
<td>ka, V, k</td>
<td>sd, md, ss</td>
<td>- N, tau</td>
</tr>
<tr>
<td>6 orall_1cpt_kavCl</td>
<td>1st order</td>
<td>1</td>
<td>ka, V, Cl</td>
<td>sd, md, ss</td>
<td>- N, tau</td>
</tr>
<tr>
<td>7 bolus_2cpt_Vkk12k21</td>
<td>IV-bolus</td>
<td>2</td>
<td>V, k, k12, k21</td>
<td>sd, md, ss</td>
<td>- N, tau</td>
</tr>
<tr>
<td>8 bolus_2cpt_CLV1QV2</td>
<td>IV-bolus</td>
<td>2</td>
<td>Cl, V1, Q, V2</td>
<td>sd, md, ss</td>
<td>- N, tau</td>
</tr>
<tr>
<td>9 infusion_2cpt_Vkk12k21</td>
<td>IV-infusion</td>
<td>2</td>
<td>V, k, k12, k21</td>
<td>sd</td>
<td>TInf, N, tau</td>
</tr>
<tr>
<td>10 infusion_2cpt_CLV1QV2</td>
<td>IV-infusion</td>
<td>2</td>
<td>Cl, V1, Q, V2</td>
<td>sd</td>
<td>TInf, N, tau</td>
</tr>
<tr>
<td>Name</td>
<td>Input</td>
<td>Cpt</td>
<td>Parameterisation</td>
<td>Administration</td>
<td>Needed Variable(s)</td>
</tr>
<tr>
<td>-----------------------</td>
<td>----------</td>
<td>-----------</td>
<td>------------------</td>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>oral_2cpt_kavkt12k21</td>
<td>1st order</td>
<td>2</td>
<td>ka, V, k, k12, k21</td>
<td>sd</td>
<td>N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
<tr>
<td>oral_2cpt_kac1v1qv2</td>
<td>1st order</td>
<td>2</td>
<td>ka, Cl, V1, Q, V2</td>
<td>sd</td>
<td>N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
<tr>
<td>bolus_3cpt_vkk12k21k13k31</td>
<td>IV-bolus</td>
<td>3</td>
<td>V, k, k12, k21, k13, k31</td>
<td>sd</td>
<td>N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
<tr>
<td>bolus_3cpt_cl1v1q2v2v3</td>
<td>IV-bolus</td>
<td>3</td>
<td>Cl, V1, Q1, V2, Q2, V3</td>
<td>sd</td>
<td>N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
<tr>
<td>infusion_3cpt_vkk12k21k13k31</td>
<td>IV-infusion</td>
<td>3</td>
<td>V, k, k12, k21, k13, k31</td>
<td>sd</td>
<td>TInf, N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>TInf, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
<tr>
<td>infusion_3cpt_cl1v1q2v2v3</td>
<td>IV-infusion</td>
<td>3</td>
<td>Cl, V1, Q1, V2, Q2, V3</td>
<td>sd</td>
<td>TInf, N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>TInf, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
<tr>
<td>oral_3cpt_kavkt12k21k13k31</td>
<td>1st order</td>
<td>3</td>
<td>ka, V, k, k12, k21, k13, k31</td>
<td>sd</td>
<td>N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
<tr>
<td>oral_3cpt_kac1v1q2v2v3</td>
<td>1st order</td>
<td>3</td>
<td>ka, Cl, V1, Q1, V2, Q2, V3</td>
<td>sd</td>
<td>N, tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>tau</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ss</td>
<td>tau</td>
</tr>
</tbody>
</table>
## Appendix I.2: PK models with Michaelis-Menten elimination

<table>
<thead>
<tr>
<th>Name</th>
<th>Input</th>
<th>Cpt</th>
<th>Parameterisation</th>
<th>Administration</th>
<th>Needed Variable(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 bolus_1cpt_VM/km</td>
<td>IV-bolus</td>
<td>1</td>
<td>V, Vm, km</td>
<td>sd</td>
<td>-</td>
</tr>
<tr>
<td>2 infusion_1cpt_VM/km</td>
<td>IV-infusion</td>
<td>1</td>
<td>V, Vm, km</td>
<td>sd</td>
<td>doseMM, TInf, m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>doseMM, TInf, tau</td>
</tr>
<tr>
<td>3 oral1_1cpt_kaVM/km</td>
<td>1st order</td>
<td>1</td>
<td>ka, V, Vm, km</td>
<td>sd</td>
<td>doseMM, m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>doseMM, TInf, tau</td>
</tr>
<tr>
<td>4 bolus_2cptVk12k21Vm/km</td>
<td>IV-bolus</td>
<td>2</td>
<td>V, k12, k21, Vm</td>
<td>sd</td>
<td>-</td>
</tr>
<tr>
<td>5 bolus_2cpt_v1qV2Vm/km</td>
<td>IV-bolus</td>
<td>2</td>
<td>v1, q, V2, Vm</td>
<td>sd</td>
<td>-</td>
</tr>
<tr>
<td>6 infusion_2cpt_Vk12k21Vm/km</td>
<td>IV-infusion</td>
<td>2</td>
<td>V, k12, k21, Vm</td>
<td>sd</td>
<td>doseMM, TInf, m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>doseMM, TInf, tau</td>
</tr>
<tr>
<td>7 infusion_2cpt_v1qV2Vm/km</td>
<td>IV-infusion</td>
<td>2</td>
<td>v1, q, V2, Vm</td>
<td>sd</td>
<td>doseMM, TInf, m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>md</td>
<td>doseMM, TInf, tau</td>
</tr>
<tr>
<td>8 oral1_2cpt_kakVk12k21Vm/km</td>
<td>1st order</td>
<td>2</td>
<td>ka, V, k12, k21,</td>
<td>sd</td>
<td>doseMM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vm, km</td>
<td>m</td>
<td>doseMM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tau</td>
</tr>
<tr>
<td>9 oral1_2cpt_kav1qV2Vm/km</td>
<td>1st order</td>
<td>2</td>
<td>ka, v1, q, V2,</td>
<td>sd</td>
<td>doseMM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vm, km</td>
<td>m</td>
<td>doseMM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>tau</td>
</tr>
<tr>
<td>10 bolus_3cpt_Vk12k13k31Vm/km</td>
<td>IV-bolus</td>
<td>3</td>
<td>V, k12, k21, k13,</td>
<td>sd</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>k31, Vm, km</td>
<td>m</td>
<td></td>
</tr>
<tr>
<td>11 bolus_3cpt_v1qV2qV3Vm/km</td>
<td>IV-bolus</td>
<td>3</td>
<td>v1, q1, V2, q2,</td>
<td>sd</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V3, Vm, km</td>
<td>m</td>
<td></td>
</tr>
<tr>
<td>12 infusion_3cpt_Vk12k13k31Vm/km</td>
<td>IV-infusion</td>
<td>3</td>
<td>V, k12, k21, k13,</td>
<td>sd</td>
<td>doseMM, TInf, m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>k31, Vm, km</td>
<td>md</td>
<td>doseMM, TInf, tau</td>
</tr>
<tr>
<td>13 infusion_3cpt_v1qV2qV3Vm/km</td>
<td>IV-infusion</td>
<td>3</td>
<td>v1, q1, V2, q2,</td>
<td>sd</td>
<td>doseMM, TInf, m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>V3, Vm, km</td>
<td>md</td>
<td>doseMM, TInf, tau</td>
</tr>
<tr>
<td>14 oral1_3cpt_kakV1k12k13k31Vm/km</td>
<td>1st order</td>
<td>3</td>
<td>ka, k12, k21, k13,</td>
<td>sd</td>
<td>doseMM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>k31, Vm, km</td>
<td>m</td>
<td>doseMM, tau</td>
</tr>
<tr>
<td>15 oral1_3cpt_kav1qV2qV3Vm/km</td>
<td>1st order</td>
<td>3</td>
<td>ka, v1, q1, V2,</td>
<td>sd</td>
<td>doseMM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>q2, V3, Vm, km</td>
<td>m</td>
<td>tau</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Drug action models</th>
<th>Null baseline</th>
<th>Baseline</th>
<th>Constant baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Name</td>
<td>Parameterisation</td>
<td>Name</td>
</tr>
<tr>
<td>Linear</td>
<td>immed_lin_null</td>
<td>Alin</td>
<td>8 immed_lin_const</td>
</tr>
<tr>
<td>Quadratic</td>
<td>immed_quad_null</td>
<td>Alin, Aquad</td>
<td>9 immed_quad_const</td>
</tr>
<tr>
<td>Logarithmic</td>
<td>immed_log_null</td>
<td>Alog</td>
<td>10 immed_log_const</td>
</tr>
<tr>
<td>Emax</td>
<td>immed_Emax_null</td>
<td>Emax, C50</td>
<td>11 immed_Emax_const</td>
</tr>
<tr>
<td>Sigmoid Emax</td>
<td>immed_gammaxnull</td>
<td>Emax, C50, gamma</td>
<td>12 immed_gammaxconst</td>
</tr>
<tr>
<td>Imax</td>
<td>immed_maxnull</td>
<td>Imax, C50</td>
<td>13 immed_maxconst</td>
</tr>
<tr>
<td>Sigmoid Imax</td>
<td>immed_gammaxnull</td>
<td>Imax, C50, gamma</td>
<td>14 immed_gammaxconst</td>
</tr>
</tbody>
</table>
### 2.2. TURNOVER RESPONSE MODELS

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

<table>
<thead>
<tr>
<th>Drug action models</th>
<th>Linear progression</th>
<th>Exponential increase</th>
<th>Exponential decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Param.</td>
<td>Name</td>
<td>Param.</td>
</tr>
<tr>
<td>Linear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 immed_lin_lin</td>
<td>Alin, S0, kprog</td>
<td>8 immed_lin_exp</td>
<td>Alin, S0, kprog</td>
</tr>
<tr>
<td>Quadratic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 immed_quad_lin</td>
<td>Alin, Aquad, S0, kprog</td>
<td>9 immed_quad_exp</td>
<td>Alin, Aquad, S0, kprog</td>
</tr>
<tr>
<td>Logarithmic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 immed_log_lin</td>
<td>Alog, S0, kprog</td>
<td>10 immed_log_exp</td>
<td>Alog, S0, kprog</td>
</tr>
<tr>
<td>Emax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 immed_Emax_lin</td>
<td>Emax, C50, S0, kprog</td>
<td>11 immed_Emax_exp</td>
<td>Emax, C50, S0, kprog</td>
</tr>
<tr>
<td>Sigmoid Emax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 immed_gammaEmax_lin</td>
<td>Emax, C50, gamma, S0, kprog</td>
<td>12 immed_gammaEmax_exp</td>
<td>Emax, C50, gamma, S0, kprog</td>
</tr>
<tr>
<td>Imax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 immed_Imax_lin</td>
<td>Imax, C50, S0, kprog</td>
<td>13 immed_Imax_exp</td>
<td>Imax, C50, S0, kprog</td>
</tr>
<tr>
<td>Sigmoid Imax</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 immed_gammaImax_lin</td>
<td>Imax, C50, gamma, S0, kprog</td>
<td>14 immed_gammaImax_exp</td>
<td>Imax, C50, gamma, S0, kprog</td>
</tr>
</tbody>
</table>
### Appendix II.3: Turnover PD models for PK/PD

<table>
<thead>
<tr>
<th>Models with impact on the output</th>
<th>Input</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of response</td>
<td>Name</td>
<td>Parameterisation</td>
</tr>
<tr>
<td>Emax</td>
<td>turn_input_Emax</td>
<td>Rin, kout, Emax, C50</td>
</tr>
<tr>
<td>Supplier</td>
<td>turn_input_gammaMax</td>
<td>Rin, kout, Emax, C50, gamma</td>
</tr>
<tr>
<td>Max</td>
<td>turn_input_gammainmax</td>
<td>Rin, kout, Emax, C50, gamma</td>
</tr>
<tr>
<td>Full</td>
<td>turn_input_gammainfull</td>
<td>Rin, kout, Emax, C50, gamma</td>
</tr>
</tbody>
</table>