



**Galeno** - Modeling and Control for Personalized Drug Administration

## Standard PK/PD Model

### Atracurium

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### Standard PK/PD Model - Atracurium

The most common models for the effect concentration of a drug are compartmental systems.

A system is a set of interconnected elements that are dependent on each other and form a unit that has specific characteristics and functions. Each system admits states that are defined as a set of variables capable to describe the system in any instant of time. Systems can be classified as continuous or discrete-time systems according to the continuous or discrete nature of the time-line over which their variables are defined. Also, systems can be classified as open, closed or isolated. An open system can exchange matter or energy with its surroundings, while a closed system can only exchange energy, but not matter with its surroundings. In contrast, an isolated system cannot exchange neither energy nor matter.

Compartmental systems are widely used to model the pharmacodynamics and pharmacokinetics of intravenously administered drugs. A compartmental system is a system that has a finite number of homogeneous, well-mixed subsystems, called compartments that exchange material among them and with the environment. These models are based on the principle of mass conservation.

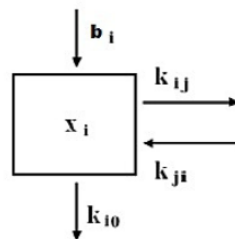


Figure 1 - Representation of a compartment.

Fig. 1 represents a compartment, in this case compartment  $i$ ; here  $b_i$  represents the input rate (the drug infusion rate to a patient if we consider the specific case of anesthesia),  $x_i$  is the concentration of material in the compartment  $i$ ,  $k_{ij}$  represents the rate of mass transfer from compartment  $i$  to compartment  $j$ , and  $k_{i0}$  represents the rate of material output from compartment  $i$  to the environment. The input to compartment  $i$ , is given by  $b_i \cdot u$ , where  $u$  is the total system input. This input, the state  $x_i$  and all the rate constants are assumed to be non-negative. At each time instant  $t$ , the variation  $\dot{x}(t)$  is the concentration of material in compartment  $i$ .

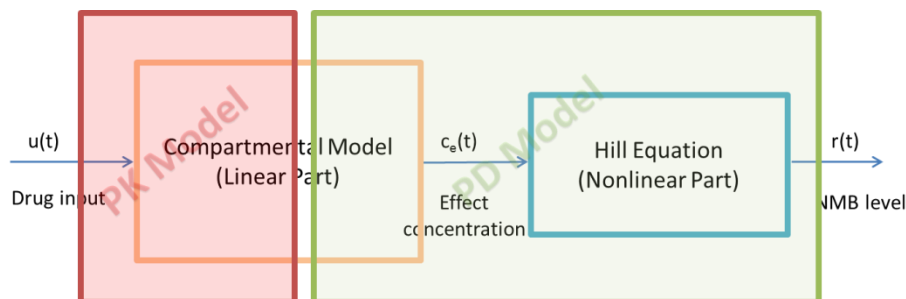


Figure 2 - Wiener Model of the Standard PK/PD Model for Atracurium



### Compartmental Model (Linear Part)

Here this model includes three compartments, where two of them represent the pharmacokinetic model (central and peripheral compartments), combined with an effect compartment which is part of the pharmacodynamic part of the model, see Fig. 3. Pharmacokinetics describes the path that a drug does inside the body, whereas pharmacodynamics means the pharmacology field that studies the physiological effects of drugs, and their mechanisms of action.

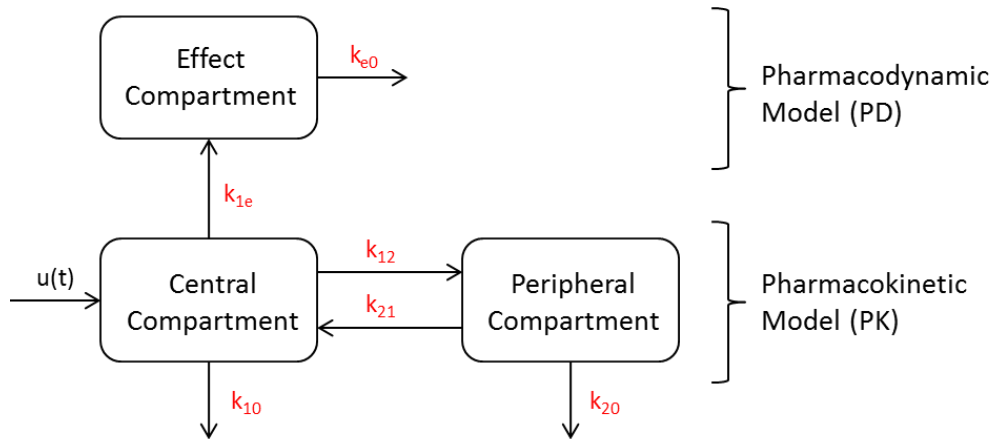


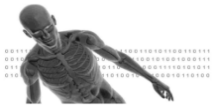
Figure 3 - Compartmental Model of the Standard PK/PD Model for Atracurium.

This model has six patient dependent parameters,  $k_{10}$ ,  $k_{12}$ ,  $k_{1e}$ ,  $k_{20}$ ,  $k_{21}$ , and  $k_{e0}$  ( $\text{min}^{-1}$ ) that must be identified for each particular patient. The state variables  $x_1$  and  $x_2$  ( $\mu\text{g/kg}$ ) correspond to the drug concentrations in central and peripheral compartments, whereas  $x_3$  ( $\mu\text{g/kg}$ ) is the drug concentration in the effect compartment, also known as effect concentration. The input  $u(t)$  ( $\mu\text{g/kg/min}$ ) corresponds to the delivery rate of drug concentration with respect to the central compartment, and is computed as  $u(t) = \tilde{u}(t)/V_1$ , where  $\tilde{u}(t)$  is the drug delivery rate, and  $V_1$  is the volume of the central compartment. The output  $y(t)$  ( $\mu\text{g/kg}$ ) corresponds to the effect concentration.

The corresponding state-space equations are as follows.

$$\underbrace{\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix}}_{\dot{x}}(t) = \underbrace{\begin{bmatrix} -(k_{12} + k_{10} + k_{1e}) & k_{21} & 0 \\ k_{12} & -(k_{21} + k_{20}) & 0 \\ k_{1e} & 0 & -k_{e0} \end{bmatrix}}_{\text{Matriz A}} \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}}_x(t) + \underbrace{\begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}}_{\text{Matriz B}} u(t)$$

$$y(t) = \underbrace{\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}}_{\text{Matriz C}} \underbrace{\begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}}_x(t)$$



### Hill Equation (Nonlinear Part)

As an output from the models presented in the previous subsection, the effect concentration,  $y(t)$ , is obtained. The effect concentration corresponds to the percentage of administered drug that will produce effect in the NMB level,  $r(t)$  (%). The relationship between the effect concentration and the NMB level is given by the Hill Equation; this is a nonlinear static equation.

$$r(t) = \frac{100}{1 + \left(\frac{y(t)}{C_{50}}\right)^\gamma},$$

where  $C_{50}$  ( $\mu\text{g/kg}$ ) and  $\gamma$  (gamma) (dimensionless) are patient-dependent parameters.

The equations obtained from the state-space equations are the following:

- $\frac{dx_1}{dt} = u(t) - x_1 \cdot (k_{12} + k_{10} + k_{1e}) + x_2 \cdot k_{21}$
- $\frac{dx_2}{dt} = x_1 \cdot k_{12} - x_2 \cdot (k_{21} + k_{20})$
- $\frac{dx_3}{dt} = x_1 \cdot k_{1e} - x_3 \cdot k_{e0}$

Since:

- $V_i c_i = x_i$
- $\frac{dC_i}{dt} = \frac{1}{V_i} \times \frac{dx_i}{dt}$

where  $V_i = 1$ :

- $\frac{dC_1}{dt} = u(t) - (k_{12} + k_{10} + k_{1e}) + k_{21}$
- $\frac{dC_2}{dt} = k_{12} - (k_{21} + k_{20})$
- $\frac{dC_3}{dt} = k_{1e} - k_{e0}$

$$\text{Effect Concentration } (C_e) - \frac{dC_e}{dt} = \frac{dC_3}{dt}$$

### Bibliography

[1] - B. C. Weatherley, S. G. Williams and E. A. M. Neill, "Pharmacokinetics, Pharmacodynamics and Dose-Response Relationships of Atracurium Administered I.V.", British Journal of Anaesthesia, 1983, 55, 39S.