Galeno - Modeling and Control for Personalized Drug Administration

Minimally Parameterized Parsimonious Model

(MPP Models)

Rocuronium

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Minimally Parameterized Parsimonious (MPP) Model - Rocuronium

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.

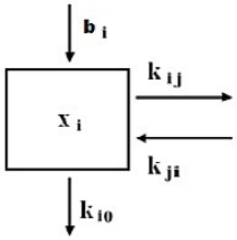

Figure 1 - Representation of a compartment.

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 $b_i.u$, 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 $\dot{\boldsymbol{x}}(\boldsymbol{t})$ is the concentration of material in compartment i.

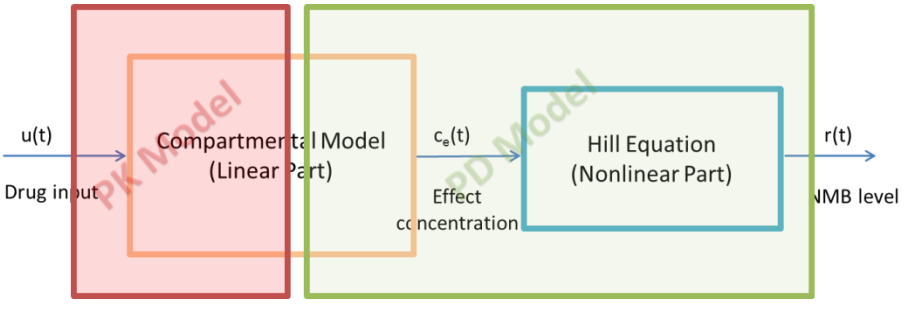

Figure 2 - Wiener Model of the MPP Model

Compartmental Model (Linear Part)

The MPP model described in [1] has been derived by system identification techniques, rather than by pharmacological considerations. It can be described as a compartmental system as seen in Fig. 3.

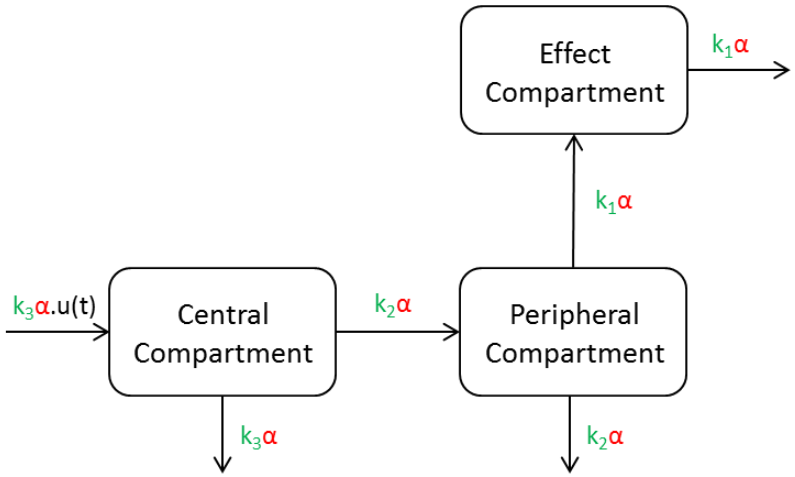

Figure 3 - Compartmental Model of the MPP Model

This model has four parameters, k_1, k_2, k_3 (min^{-1}) and α (alpha) (dimensionless) that, as in the previous case, must be identified for each particular patient. However good results are obtained if the parameters k_1, k_2, k_3 are fixed, based on previous knowledge on the patient population, and only is identified for each particular patient. This constitutes a great advantage. The values of k_1, k_2 and k_3 used in the sequel are $k_1 = 1$, $k_2 = 4$ and $k_3 = 10$, [2]. The state variables x_1 and x_2 (μg/kg) correspond to the drug concentrations in compartments 1 and compartment 2, whereas x_3 (μg/kg) is the drug concentration in the compartment 3, also known as effect concentration. The input u(t) (μg/kg/min) corresponds to the drug delivery rate 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) (μg/kg) corresponds to the effect concentration.

The corresponding state-space equations are as follows.

$$\underbrace{\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\\ \dot{x}_3\end{bmatrix}}_{\dot{x}}(t) = \underbrace{\begin{bmatrix}-k_3\alpha & 0 & 0\\ k_2\alpha & -k_2\alpha & 0\\ 0 & k_1\alpha & -k_1\alpha\end{bmatrix}}_{Matriz\ A}\underbrace{\begin{bmatrix}x_1\\ x_2\\ x_3\end{bmatrix}}_{x}(t) + \underbrace{\begin{bmatrix}k_3\alpha\\ 0\\ 0\end{bmatrix}}_{Matriz\ B}u(t)$$

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

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} (µg/kg) is a fixed parameter equal to 1 and γ (gamma) (dimensionless) is a patient-dependent parameter.

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

- $\frac{dx_1}{dt} = u(t)k_3\alpha - x_1.k_3\alpha$
- $\frac{dx_2}{dt} = x_1.k_2\alpha - x_2.k_2\alpha$
- $\frac{dx_3}{dt} = x_2.k_1\alpha - x_3.k_1\alpha$

Since:

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

where $V_i = 1$:

- $\frac{dC_1}{dt} = u(t)k_3\alpha - k_3\alpha$
- $\frac{dC_2}{dt} = k_2\alpha - k_2\alpha$
- $\frac{dC_3}{dt} = k_1\alpha - k_1\alpha$

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

Bibliography

[1] - M. M. Silva, R. Rabiço, T. Mendonça and T. Wigren, ” **Control of rocuronium-induced neuromuscular blockade via online identification of a two-parameters Wiener model"**, 16th IFAC Symposium on System Identification, Brussels, Belgium, July, 2012.

[2] - M. M. Silva, **“Prediction error identification of minimally parameterized wiener models in anesthesia”**, in 18th IFAC World Congress, Milano, Italy, Aug 2011.