Galeno - Modeling and Control for Personalized Drug Administration

Schnider Model

Propofol

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Schnider Model - Propofol

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.

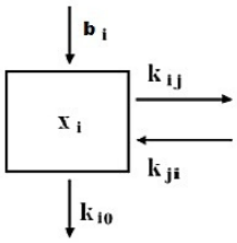

Figure 1 - Representation of a compartment.

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.

Compartmental Model (Linear Part)

Here this model includes three compartments, where both represent the pharmacokinetic model (central and peripheral compartments). These compartments are 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.

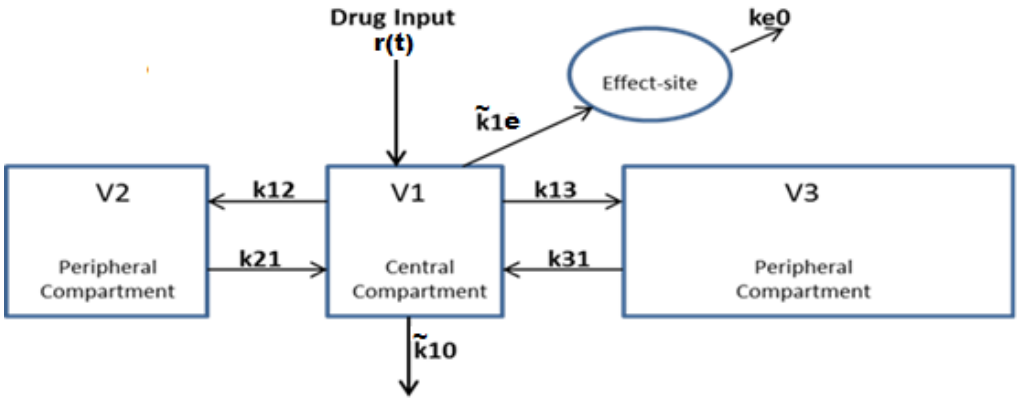

Figure 2 - Compartmental Model of the Schnider Model for Propofol.

This model has seven patient dependent parameters: $\tilde{k}_{10}$, $\tilde{k}_{1e}$, with $(k_{10} = \tilde{k}_{10} + \tilde{k}_{1e})$, k_{12}, k_{13}, k_{21}, k_{31}, and k_{e0} (min^{-1}) that must be identified for each particular patient. The variables V_1, V_2, and V_3 (mL) correspond to the volume of the central and peripheral compartments, respectively. The state variables C_1, C_2 and C_3 (µg/mL) correspond to the drug concentrations in central and peripheral compartments, whereas C_e (µg/mL) is the drug concentration in the effect compartment, also known as effect concentration. The input u(t) (µg/min) corresponds to the delivery rate of drug concentration with respect to the central compartment. The output y(t) (µg/mL) corresponds to the effect concentration.

- Value of the variables for the Schnider Model:

  - V_1 = 4.27 [L];
  - V_2 = (18.9 - 0.391*(age - 53)) [L];
  - V_3 = 238 [L];

  - k_{10} = 0.443 + 0.0107*(weight-77)-0.0159*(LBM-59) + 0.0062*(height-177) [min^{-1}];
  - k_{12} = 0.302 - 0.0056*(age - 53) [min^{-1}];
  - k_{13} = 0.196 [min^{-1}];
  - k_{21} = (1.29 - 0.024*(age - 53))/(18.9 - 0.391*(age -53)) [min^{-1}];
  - k_{31} = 0.0035 [min^{-1}];
  - k_{e0} = 0.456 [min^{-1}];

LBM formula:

- Male: 1.10*weight(kg) - 128*weight(kg)^2/height(cm)^2;
- Female: 1.07*weight(kg) - 148*weight(kg)^2/height(cm)^2;

The corresponding state-space equations are as follows.

$$\begin{bmatrix}\dot{c}_1\\ \dot{c}_2\\ \dot{c}_3\\ \dot{c}_e\end{bmatrix}(t) = \underbrace{\begin{bmatrix}-(k_{10}+k_{12}+k_{13}) & \frac{V_2}{V_1}k_{21} & \frac{V_3}{V_1}k_{31} & 0\\ \frac{V_1}{V_2}k_{12} & -k_{21} & 0 & 0\\ \frac{V_1}{V_3}k_{13} & 0 & -k_{31} & 0\\ k_{e0} & 0 & 0 & -k_{e0}\end{bmatrix}}_{Matriz\ A}.\underbrace{\begin{bmatrix}c_1\\ c_2\\ c_3\\ c_e\end{bmatrix}}_{x}(t) + \underbrace{\begin{bmatrix}1/V_1\\ 0\\ 0\\ 0\end{bmatrix}}_{Matriz\ B}.u(t)$$

$$y(t) = \underbrace{[0 \quad 0 \quad 0 \quad 1]}_{Matriz\ C}\underbrace{\begin{bmatrix}c_1\\ c_2\\ c_3\\ c_e\end{bmatrix}}_{x}(t)$$

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

$\frac{dQ_1}{dt} = r(t) + Q_2k_{21} + Q_3k_{31} - Q_1\left(\tilde{k}_{10} + k_{12} + k_{13} + \tilde{k}_{1e}\right)$, com $\tilde{k}_{10} + \tilde{k}_{1e} = k_{10}$;

$\frac{dQ_2}{dt} = Q_1k_{12} - Q_2k_{21}$;

$\frac{dQ_3}{dt} = Q_1k_{12} - Q_3k_{31}$;

$\frac{dQ_e}{dt} = Q_1\tilde{k}_{1e} - Q_ek_{e0}$

$Q_e = V_e.C_e \xrightarrow{yields} V_e\frac{dC_e}{dt} = V_1.C_1\tilde{k}_{1e} - V_e.C_ek_{eo}$

$\dot{C}_e = \frac{V_1}{V_e}\tilde{k}_{1e}C_1 - C_ek_{eo}$

once:

$$\lim_{t\to\infty} C_e(t) = \lim_{t\to\infty} C_1(t) \Rightarrow \lim_{t\to\infty} \dot{C}_e(t) = 0$$

$$\frac{V_1}{V_e}C_1\tilde{k}_{1e} = C_ek_{eo} \Rightarrow \frac{V_1}{V_e}C_e\tilde{k}_{1e} = C_ek_{eo} \Rightarrow \boxed{\frac{V_1}{V_e}\tilde{k}_{1e} = k_{eo}}$$

and so:

- $\frac{dQ_1}{dt} = r(t) + Q_2k_{21} + Q_3k_{31} - Q_1(k_{10} + k_{12} + k_{13})$
- $\frac{dQ_2}{dt} = Q_1k_{12} - Q_2k_{21}$
- $\frac{dQ_3}{dt} = Q_1k_{12} - Q_3k_{31}$
- $\frac{dQ_e}{dt} = Q_1k_{e0} - Q_ek_{e0}$ Since:

Representantion of the concentration in each compartment:

$V_ic_i = Q_i$

$\frac{dC_i}{dt} = \frac{1}{V_i} \times \frac{dQ_i}{dt}$

And finally:

$$\frac{dC_1}{dt} = r(t).\frac{1}{V_1} + k_{21}C_2(t).\frac{V_2}{V_1} + k_{31}C_3(t).\frac{V_3}{V_1} - (k_{10} + k_{12} + k_{13})C_1(t)$$

$$\frac{dC_2}{dt} = k_{12}C_1(t).\frac{V_1}{V_2} - k_{21}C_2(t)$$

$$\frac{dC_3}{dt} = k_{13}C_1(t).\frac{V_1}{V_3} - k_{31}C_3(t)$$

$$\frac{dC_e}{dt}(t) = k_{e0}C_1(t) - k_{e0}C_e(t)$$

Plasmatic Concentration - C_p

$$\frac{dC_p}{dt}(t) = \dot{C}_1(t)$$

Effect Concentration - C_e

$$\frac{dC_e}{dt}(t) = k_{e0}C_1(t) - k_{e0}C_e(t)$$

Bibliography

[1] - Thomas W. Schnider, Charles F. Minto, Pedro L. Gambús, Corina Andresen, David B. Goodale, Steven L. Shafer and Elizabeth J. Youngs, ”**The Influence of Method of Administration and Covariates on the Pharmacokinetics of Propofol in Adult Volunteers"**, Anesthesiology, 1998, 88, 1170-82.