C15 Clearance Identification - Definition

Simulation and Identification of a Model for Renal Clearance

This comparison is a practical model approach in the field of physiological simulation. It was originally introduced to improve medical analysis of the renal clearance (for further informations refer to Short Note *Renal Clearance – Modelling and Identification*, SNE 35/36, November 2002, p. 42-44).

The renal clearance i.e. the possibility of the kidney to transport a given substance or marker is investigated. To estimate the renal clearance a marker is injected. For a certain time control samples of the concentration of the marker are done. Then a two-compartment model has to be identified with these experimental marker concentration profiles.

Model Equations

In the compartment model the extracellular space is considered to be composed of two functionally separated spaces, a well perfused central volume and a less perfused peripheral compartment. The marker kinetics as represented by the temporal courses of the marker amounts in the two compartments is the result of the infusion strategy, the exchange transports between the two compartments, and finally the renal elimination process (1,2,3).

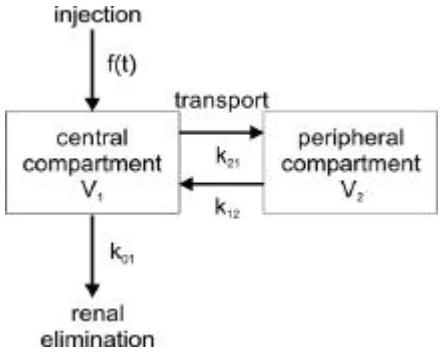

Figure 1: Compartment Model

The model can be formulated by a set of two simultaneous differential equations describing the rates of change of the marker amounts in the two respective compartments:

$$dx_1/dt = f(t) - (k_{01} + k_{21})x_1 + k_{12}x_2 \quad (1)$$

$$dx_2/dt = k_{21}x_1 - k_{12}x_2 \quad (2)$$

$$f(t)=D/\tau, \qquad 0 \le t < \tau \quad (3)$$

$$c(t) = x_1(t) / V_1 \quad (4)$$

Equations (1) and (2) can be stated verbally in the following way: Firstly, the rate of change of the marker amount in the central compartment, dx_1/dt, is determined by the input strategy chosen, the loss of marker from the central to the peripheral compartment, its gain by the central from the peripheral volume, and its elimination through the renal excretion mechanism. The renal clearance C is defined as $C = k_{01} V_1$.

Secondly, the rate of change of the marker amount in the peripheral space, dx_2/dt, is due to gain from and loss to the central pool. These processes are assumed to be proportional to the marker amounts momentarily contained in the respective distribution.

Data

Not only the amount of the injected marker D can vary but also the time of the injection τ can differ between seconds an hours. The parameters k_{01}, k_{21}, k_{12}, and V_1 may be given, but normally – as mentioned before - it is the task to find those parameters by adapting the system to given concentrations c(t). Note, that also V_1, the conatnt volume in the central compartment, is an unknown parameter.

The following test data resulted from a test which lasted for 4 hours and should be used for identification of the four parameters k_{01}, k_{21}, k_{12}, and V_1.

Time	Concentration
5 min.	276 mg/l
10 min.	227 mg/l
15 min.	203 mg/l
20 min.	190 mg/l
25 min.	184 mg/l
30 min.	174 mg/l
35 min.	176 mg/l
40 min.	171 mg/l
45 min.	167 mg/l
50 min.	163 mg/l
55 min.	151 mg/l
1 hr.	155 mg/l
1 hr. 15 min.	150 mg/l
1½ hrs.	142 mg/l
1 hr. 45 min.	141 mg/l
2 hrs.	135 mg/l
2½ hrs.	128 mg/l
3 hrs.	120 mg/l
4 hrs.	111 mg/l

Table 1: Meassured Concentrations c(t)

Methods

Adaption to the given experimental data should be done with the least square method. For the set of parameters $p = (k_{01}, k_{21}, k_{12}, V_1)$ we can do this by searching the minimum of the criterion:

$$E(p)= \sum(c_1(t_i) - c_{exp}(t_i))^2, (i = 1\ldots n) \qquad (5)$$

The identification of the model should be done with an appropriate algorithm, e.g. with the Levenberg-Marquardt algorithm, allowing to estimate the optimal values of the independent system parameters k_{01}, k_{21}, k_{12}, and V_1 as well as of dependent parameters such as V_2 or the clearance $C = k_{01} V_1$.

The error estimation of the parameters done with a Monte Carlo method, is processed with statistics of a number of adapted "artificial" data, which one gets by superposition of random numbers with mean of 0 and standard deviation

$$s= (E/(n-n_p))^{½} \qquad (6)$$

on the given data. n ist the number of experimental data and n_p the number of parameters = 4.

Model Approach

Although the system of linear differential equations can be solved analytical, the problem also can be solved numerical. Furthermore, for other markers the constant parameter k_{01} becomes a function $k_{01}(c(t))$ of the concentration, so that the model becomes nonlinear and cannot be solved analytically.

Give a short explanation of the model approach and implementation, especially give details on bolus modelling. For comparison with the analytic solution see also the Short Note Short Note *Renal Clearance – Modelling and Identification*, SNE 35/36, November 2002, p. xx-xx

Task a: Simulation of the System

Implementation of the model with given parameters, where k_{01}=0.0041, k_{12}=0.0585, k_{21}=0.0498, and V_1=7.3; $x_1(0) = x_2(0) = 0$.

Simulate the system for 240 minutes and assume three different time values for the bolus injection (take that the jumps of the bolus function are implemented correctly, in order to get correct results):

- $D_1 = 2500$, $\tau_1 = 0.5$ min
- $D_2 = 2500$, $\tau_2 = 3$ min.
- $D_3 = 2500$, $\tau_3 = 240$ min.

- Plot the solution and for τ_1 the difference between the concentration of the injection and the real concentration.
- Give the values of x_1 one minute after the injection ends, in case of $\tau = 240$ min at the end of the injection time.

Task b: Identification

The model should be fitted to the experimental data mentioned above (see Table 1 and Figure 2). Evaluation of the cost functionn (criterion (5)) requires simulation of the system for 240 minutes, with type 1 bolus injection (D = 2500, $\tau = 0.5$ min).

The identification of the model should be done with an appropriate algorithm, e.g. with the Levenberg-Marquardt algorithm.

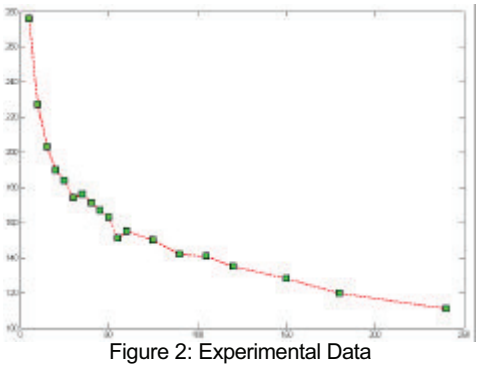

Figure 2: Experimental Data

Take care that the numerical function is evaluated at exactly the same points the experimental data is measured. Explain how the model is implemented (differential equation and Identification).

- Give the identified the values for k_{01}, k_{21}, k_{12}, and V_1, the maximum of the function, the clearance C and the residuum.
- Plot the data points and the solution of the identification problem.

Task c: Error Estimation

Perform 1000 times the identification (simulation) with different „artificial" data sets computed with the method mentioned above (formula (6)), resulting in 1000 parameters sets $(k_{01}, k_{21}, k_{12}, V_1)$.

Give mean and deviation of the parameters k_{01}, k_{21}, k_{12}, , and V_1 .

Further info: www.argesim.org/comparisons

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