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# About one inverse problem in pharmacokinetics

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# 1. Introduction

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- The density function $F(t)$ of transit times characterizes the body with respect to the transport of drug, i.e. $F(t)$ determines the transport function of the control system.
- The output, i.e. the time course of the plasma concentration $C(t)$ at the exit is the result of dosage flow (input) $G(t)$ and the transport function $F(t)$:

$$C(t) = \int_0^t G(\tau)F(t-\tau)d\tau. \qquad (1)$$



## 2. Compartment models

If a dose of drug is applied to the body by means of a bolus injection, the input $G(t)$ may be considered as a $\delta$-impulse and all molecules enter that system (body) at the same time. They leave the body according to the distribution of transit times.

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The function $F(t)$ then can be derived by application of classic compartment modeling to the experimental plasma concentration after intravenous (i.v) input. The data points can be fitted to sum of exponents:

$$C^{i.v.}(t) = \sum_{i=1}^{n} A_i e^{-\alpha_i t}, \qquad (2)$$

where $n$ is the number of compartments, $C^{i.v.}(t)$ represents the plasma concentration at time $t$. $A_i$ and $\alpha_i$ are positive constants, which characterize the drug kinetic 1).



| Time | C | Delta |
|---|---|---|
| 0.02 | 6.16 | 1.83 |
| 0.05 | 4.01 | 1.49 |
| 0.08 | 3.36 | 0.76 |
| 0.17 | 2.96 | 1.16 |
| 0.33 | 2.26 | 0.6 |
| 0.67 | 1.47 | 0.55 |
| 1 | 0.63 | 0.13 |
| 2 | 0.32 | 0.006 |

Table 1: Intravenous application of EMOVIT

Concentrations measured in the blood after intravenous application of the drug to 10 patients.

In the third column the standard deviations of the measurements are presented.

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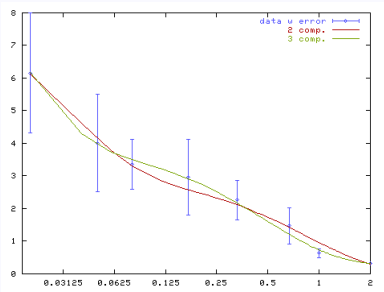


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The time is on logarithmic scale.

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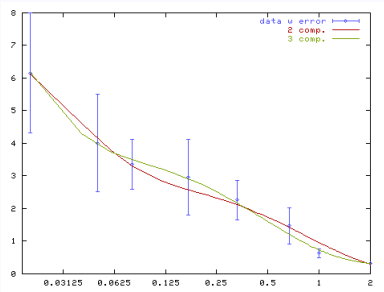
(3)

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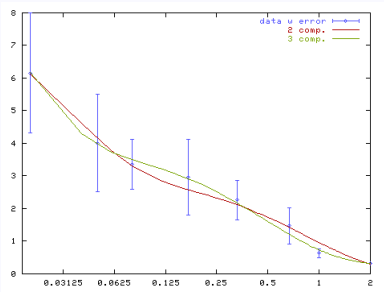


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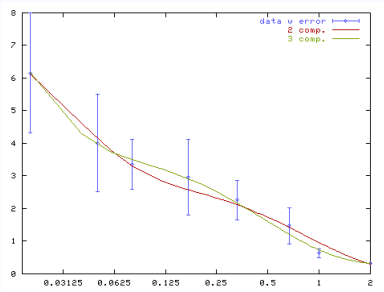
The values of estimated parameters:

$$\begin{aligned} A_1 &= 5.74 \quad A_2 = 3.12 \\ \alpha_1 &= 31.28 \quad \alpha_2 = 1.17 \end{aligned} \tag{3}$$

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Therefore, the output concentration $C^{i.v.}(t)$ is directly proportional to the density function $F(t)$ of the transit times:

$$F(t) = \frac{C^{i.v.}(t)}{\int_0^\infty C^{i.v.}(t)dt} = \frac{C^{i.v.}(t)}{\sum_{i=1}^{n} \frac{A_i}{\alpha_i}}. \qquad (3)$$

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| Time | C | Delta |
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| 0 | 0 | 0.0 |
| 0.08 | 1.441 | 1.475 |
| 0.33 | 1.873 | 0.782 |
| 0.5 | 2.333 | 0.948 |
| 1.0 | 2.23 | 0.514 |
| 1.5 | 1.777 | 0.744 |
| 2.0 | 1.48 | 0.879 |
| 3.0 | 0.607 | 0.298 |
| 6.0 | 0.1 | 0.1 |

Table 2: Oral application of EMOVIT

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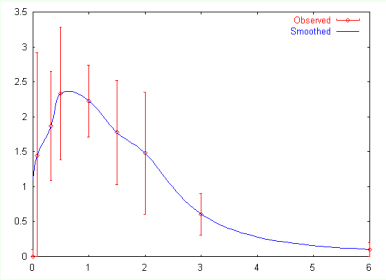
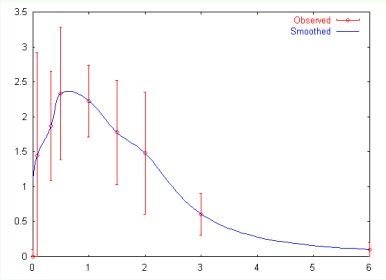



The problem is to estimate the input function $G(t)$ by given:

Figure 2: Smothed oral data

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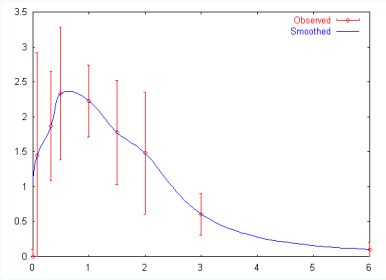
- $N$ data points of plasma concentration $C_i = C^{noni.v.}(t)$, $(i = 1, 2, ..., N)$, determined experimentally as an average value after oral application of the drug to 10 individuals in the moment $t_i$;

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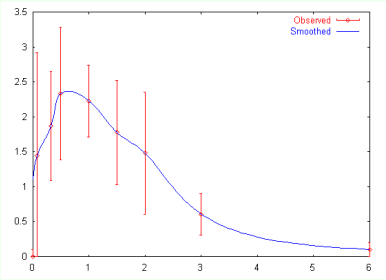


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- the standard deviation $\delta$ of the individual measurement;
- estimated from (3) body transport function $F(t)$.

# 4. Splines

For solving equation 1 an appropriate deconvolution procedure is employed. The function $G(t)$ is sought in the form of cubic spline with $m+1$ knots ($m \leqslant N$):

$$G_i(\tau) = G_i^0 + G_i^1 (\tau - T_{j-1}) + G_i^2 (\tau - T_{j-1})^2 + G_i^3 (\tau - T_{j-1})^3 ,$$



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where *j=1,2,...,m* , $T_j \in [0,\ t_N]$ are knots, $\tau \in [T_{j-1}, T_j]$ and $G_j^s, s = 0, 1, 2, 3$ are unknown spline coefficients.



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$$\left| \begin{array}{l} G_{j-1}(T_j) = G_j(T_j), \\ G'_{j-1}(T_j) = G'_j(T_j), \\ G''_{j-1}(T_j) = G''_j(T_j), \end{array} \right.$$

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where *j=2,...,m* and $G_1(0) = G_1''(0) = 0$.

Then for every $t_i \in [T_{l-1}, T_l],\ i = 1, 2, ..., N,\ l = 1, 2, ...., m$ from (1) and (4) it follows:

$$C(t_i) = \sum_{j=1}^{i-1} \sum_{s=0}^{3} G_j^s \int_{T_{j-1}}^{T_j} (\tau - T_j)^s F(t_i - \tau)\, d\tau$$

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Obviously (6) represents a linear system of $N$ equations with $4m$ unknown quantities $g_1 = G_1^0,\ g_2 = G_1^1,\ g_3 = G_1^2,\ g_4 = G_1^3,\ g_5 = G_2^0,\ , ..., g_{4m} = G_m^3$:

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$$XG = C, \qquad (7)$$

where $X$ is the matrix of coefficients calculated from (6) by exact computation the integrals, $G = (g_1, g_2, ..., g_{4m})'$, $C = (C_1, C_2, ..., C_N)'$ ,({$\prime$}- transpose of a matrix).

The conditions (5) in a matrix form could be written as

$$AG = 0, \tag{8}$$

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$$\Phi = (C - XG)' W (C - XG), \tag{9}$$

where $W = DRD$ is $N \times N$ dimensional matrix, $D$ is a diagonal matrix, which elements are $\delta_i$ and $R$ is correlation matrix of data vector $C$.







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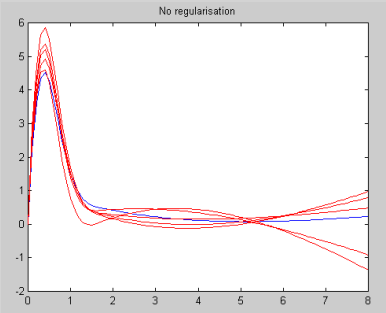
After minimization of (9) it follows that

$$G = \left(X'W^{-1}X + A'A\right)^{-1} X'W^{-1}C. \tag{10}$$



# 5. Simulation




Let the experimental data are perturbed

$$Y_{(p)} = C + \theta_p \delta, \ (p = 1, 2, ...),$$

where $\delta = (\delta_1, \delta_2 ..., \delta_N)'$ and $\theta_p$ are random numbers $|\theta_p| \leqslant 1$.

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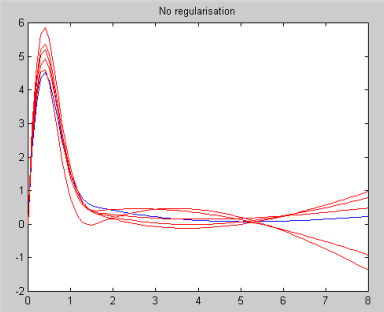


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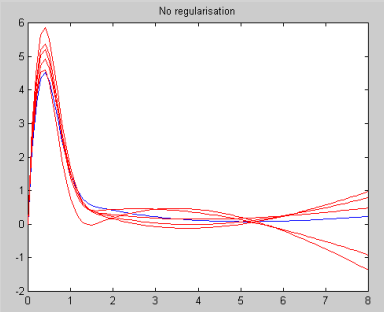


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On Fig. 3 the right side of (1) with perturbations ( p = 5 ) and solutions $G_{(p)}$ are presented.

The estimated data points $C_i$ with $\delta_i$ are from plasma concentrations after oral application of psycho therapeutic drug EMOVIT.

## 6. Stabilization

For finding the generalized solution of (1) (quasi-solution 3)), which is stable with respect to small perturbation of the right side of (1), the following algorithm is proposed.

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is introduced, where $\alpha > 0$ is parameter of regularization , $\Omega(G)$ is appropriate chosen stabilizing functional. The function $G(t)$ is sought by the condition of minimizing the functional (11)

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$$G^{\alpha} = \left(X'W^{-1}X + A'A + \alpha\Omega\right)^{-1} X'W^{-1}C. \tag{12}$$

In the concrete case $\Omega$ has the form

$$\Omega(G) = \int_{\beta}^{t_N} \left[G''(\tau)\right]^2 d\tau, \tag{13}$$

where $\beta \in [0,\ t_N]$ is a parameter, which controls the smoothing of the splines (4).

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where $\beta \in [0,\ t_N]$ is a parameter, which controls the smoothing of the splines (4). For fixed $T_{j-1} \leqslant \beta \leqslant T_j$ $(j = 1, 2, ..., m)$, (13) obtains the form

$$\Omega(G) = \sum_{q=j}^{m} \left[4\left(G_q^2\right)^2 \Delta_q + 12 G_q^2 G_q^3 \left(\Delta_q\right)^2 + 12\left(G_q^3\right)^2 \left(\Delta_q\right)^3\right], \tag{14}$$

where $\Delta_q = T_q - T_{q-1}$.

The quantity of $\alpha$ is determined according suggestion in 3) by using the error estimation

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as follows

$$\rho = (XG^{\alpha}, C) = \varepsilon,$$

where $\rho$ is the distance of Mahalanobis 4):

$$\rho(U, V) = \left[(U - V)'(U - V)\right]^{\frac{1}{2}}.$$



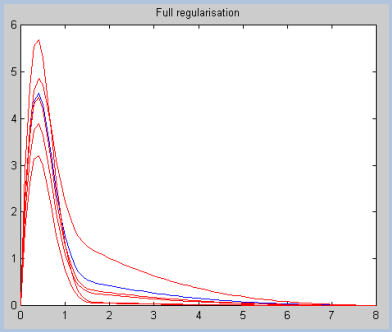
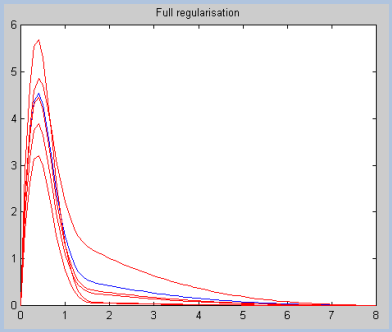



Fig.4 shows the stabilized quasi-solution $G^{\alpha}$, obtained for $\alpha = 0.06$ and $\beta = 0.89$ from experimental data of EMOVIT.

Figure 4: Full regularization

The proposed method offers better and more stimulating information about the drug absorption process, which is not observable and therefore shows some new ways in pharmacokinetical investigations.

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[2] Scheffe H.: *The Analysis of Variance*, JW, New York, 1963.

[3] Tikhonov A.N., Arsenin V.J.: *Methods of Solution of Ill-Posed Problems*, N, Moscow, 1974 (in Russian).

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# References


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