About one inverse problem in pharmacokinetics

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Abstract

In the paper one ill posed problem from pharmacokinetics is studied. The human body is assumed to be a control system. The transit times of drug molecules are considered as independent random variables with the same distribution function. The corresponding density function is considered as a transport function of the system.

First the parameters of the parameters of the transport function are estimated given the observations on the plasma concentrations after intravenous application of the drug. This is done in the usual way using compartment models.

The question is how to recover the input function (absorption process) given the observations on the plasma concentrations (output of the system) after non intravenous application of the drug (oral, muscular, subcutaneous, etc.).

The input function is estimated using cubic splines. The result is stabilized using Tikhonov regularization.

The method is applied on data from bulgarian medicine EMOVIT.

1 Introduction

The body is assumed as a control system. The transit times of the drug molecules are considered as i.i.d. random variables. 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 at the exit is the result of dosage flow (input) $G(t)$ and the transport function:

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

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 δ-impulse and all molecules enter that system (body) at the same time. They leave the body according to the distribution of transit times.

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:

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

where n is the number of compartments, $C^{i.v.}(t)$ represents the plasma concentration at time t. A_i and α_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.

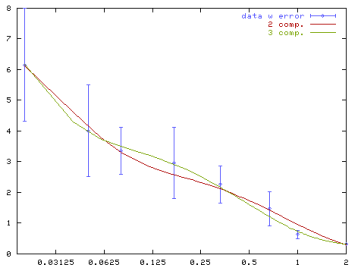


Figure 1: Estimated observation using compartment models

On the picture we see the observed plasma concentrations and estimated transport function using 2- and 3- compartment models.
The time is on logarithmic scale.
The choice of simpler 2-compartment model was made using F-test.

The values of estimated parameters:

$$\begin{array}{llll} A_1 & = 5.74 & A_2 & = 3.12 \\ \alpha_1 & = 31.28 & \alpha_2 & = 1.17 \end{array}$$

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

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

3 The Problem of Unknown Input

When the application of the drug is non intravenous (i.e. is oral, muscular, subcataneous etc.), the input function $G(t)$ (absorption process) is unknown.

Time	C	Delta
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

Concentrations measured in the blood after oral application of the drug to the same 10 patients.
In the third column the standard deviations of the measurements are presented. They are too big.

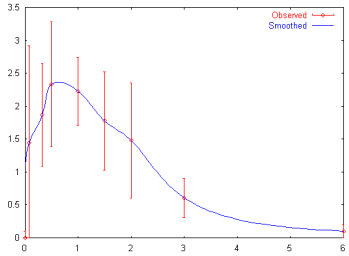


Figure 2: Smothed oral data

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

- 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;
- the standard deviation δ 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 ($m \leqslant N$):

$$G_i(\tau) = G_i^0 + G_i^1 (\tau - T_{j-1}) + G_i^2 (\tau - T_{j-1})^2 + G_i^3 (\tau - T_{j-1})^3, \qquad (4)$$

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. The cubic splines (4) satisfy the following conditions:

$$\left| \begin{array}{l} G_{j-1}(T_j) = G_j(T_j), \\ G'_{j-1}(T_j) = G'_j(T_j), \\ G''_{j-1}(T_j) = G''_j(T_j), \end{array} \right. \qquad (5)$$

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:

$$C(t_i) = \sum_{j=1}^{i-1} \sum_{s=0}^{3} G_j^s \int_{T_{j-1}}^{T_j} (\tau - T_j)^s F(t_i - \tau)\, d\tau + \sum_{s=0}^{3} G_l^s \int_{T_{l-1}}^{t_i} (\tau - T_{l-1})^s F(t_i - \tau)\, d\tau. \qquad (6)$$

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

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

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

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

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

where A is $3(m-1) \times 4m$ dimensional matrix.

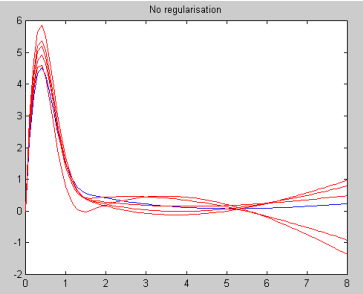
For finding the unknown spline coefficients of G , the least square estimation (2) is used. They are obtained by the conditions for minimizing the functional

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

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

After minimization of (9) it follows

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



Let the experimental data are perturbed

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

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

Figure 3: No regularization

The solutions $G_{(p)}$ of (10), where now C is $Y_{(p)}$, show instability I in the sense of Tikhonov (3).

On Fig. 1 and Fig. 2 are presented respectively the right side of (1) with perturbations (p = 5) and solutions $G_{(p)}$. The estimated data points C_i with δ_i are from plasma concentrations after oral application of psycho therapeutic drug EMOVIT.

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.

The functional

$$M^{\alpha}[G] = \Phi + \alpha\Omega(G) \tag{11}$$

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)

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

In the concrete case Ω 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). 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 α is determined according suggestion in (3) by using the error estimation

$$\varepsilon = \frac{1}{N}\sqrt{\sum_{i=1}^{N} \delta_i^2}$$

as follows

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

where ρ is the distance of Mahalanobis (4):

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

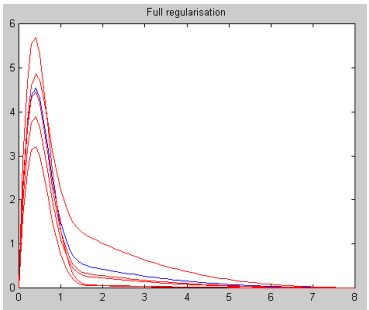


Fig.4 shows the stabilized quasi-solution G^{α}, obtained for $\alpha = 0.06$ and $\beta = 0.89$ from experimental data of EMOVIT.

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.

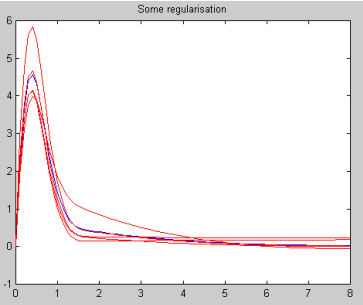


Figure 5: Some regularization

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