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Identification of the parameters in mathematical models of BSP kinetics in the human liver

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Identifikace parametrů matematických modelů BSP-kinetiky v lidských játrech

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Contents

1. Introduction

The evolution of computer science has supported the development of many areas of research, e.g. in physics, chemistry, medicine and mathematics. Identification theory belongs to these areas. This theory started to be developed in the sixties of the 20th century. At first the identification techniques for linear systems were developed, R. Bellman and K. J. Åstrőm proposed the methods based on the Laplace transform, J. Delforge prefered the modal matrix approach.

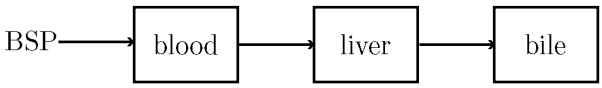
A number of biological or economical processes can't be described by linear systems. The techniques for parameter determination of the nonlinear systems depend on the model structure. L. Zhao and Y. Lu employ the least square method for the identification of deterministic and stochastic systems. The quasilinearization method is the most important one for the identification of nonlinear differential systems.

In the submited thesis, classical quasilinearization, its employing for the inverse problems and its modification for the parameter identification are presented (chapter 4).

The aim of this work is to determine the parameters characterizing systems of ordinary differential equations. These systems describe the liver function using the BSP-test (chapter 5). Properties of the systems are analyzed in chapter 6. The uniqueness of the parameter determination is discussed in chapter 7. In the chapter 8 we present the clinical data and chapter 9 is devoted to the numerical results based on them.

2. Mathematical models

The BSP (Bromsulphtalein) dynamical test is employed for quantitative assesing of the liver function. BSP is a hepatotrophic matter, which is injected into the blood. The liver is the only organ in the body which takes BSP and secrets it directly into the bile. We can represent this process by a three compartment model.



The extraction of BSP can be described by systems of ordinary differential equations.

A simple model of the process describing the extraction of BSP in these individual compartments (the blood, the liver and the bile) can be given by a system of linear ordinary differential equations (JLM) [22]

$$\begin{aligned} x'(t) &= -a_1 x + a_2 y, \\ y'(t) &= a_1 x - (a_2 + a_3) y, \\ z'(t) &= a_3 y, \end{aligned} \tag{2.1}$$

where

$x(t)$	is the amount of BSP (mg) in the blood at the time t,
$y(t)$	is the amount of BSP (mg) in the liver at the time t,
$z(t)$	is the amount of BSP (mg) in the bile at the time t,
a_1, a_2, a_3	are the transfer rate constants (min^{-1}).

Suppose that some quantity $I > 0$ (mg) of BSP is injected into the blood at once. This leads to the initial condition

$$x(0) = I,\ y(0) = z(0) = 0. \tag{2.2}$$

The hepatotrophic matter is cumulated in the liver. This organ is able to take in only a limited amount of BSP, i.e. the liver has some capacity $K > 0$. In this case the process of extraction can be described by the simple nonlinear system of ordinary differential equations (JNM)

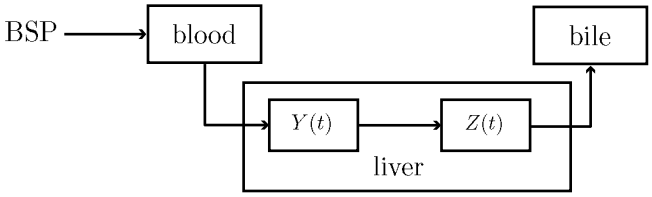
$$\begin{aligned} x'(t) &= -b_1 x(K-y), \\ y'(t) &= b_1 x(K-y) - b_2 y, \\ z'(t) &= b_2 y, \end{aligned} \tag{2.3}$$

with the initial condition (2.2).

BSP is "working" inside the hepatic cells. Suppose that the rate of transfer from blood to the liver is changing, when passing through the cell's membrane. Denote

$X(t)$	is the amount of BSP (mg) in the blood at the time t,
$Y(t)$	is the amount of BSP (mg) in the membranes of hepatic cells at the time t,
$Z(t)$	is the amount of BSP (mg) inside the cells at the time t,
d_1, d_2, d_3, d_4	are the transfer rate constants (min^{-1}).

Now we represent the extraction of BSP by the four compartment model:



This situation can be described by the system of linear diferential equations (LM)

$$\begin{aligned} X'(t) &= -d_1 X + d_2 Y, \\ Y'(t) &= d_1 X - (d_2 + d_3) Y, \\ Z'(t) &= d_3 Y - d_4 Z, \\ V'(t) &= d_4 Z \end{aligned} \tag{2.4}$$

with initial condition

$$X(0) = I,\ Y(0) = Z(0) = V(0) = 0. \tag{2.5}$$

If we consider the capacity of the liver, then we can describe the extraction from the respective components of the model by the system of nonlinear diferential equations (NM) [15]

$$\begin{aligned} X'(t) &= -c_1 X(K_1 - Y), \\ Y'(t) &= c_1 X(K_1 - Y) - c_2 Y(K_2 - Z), \\ Z'(t) &= c_2 Y(K_2 - Z) - c_3 Z, \\ V'(t) &= c_3 Z, \end{aligned} \tag{2.6}$$

where K_1 is the capacity of the cell's membranes, K_2 denotes the capacity of the interior of the cells, and c_1, c_2, c_3 are the rates transfer constants.

All the parameters characterizing the systems are unknown.

3. Clinical data

To determine the unknown parameters (the capacities and the rate transfer constants) we employ the measured data. In the first table there are presented measurements of the decay of BSP from the blood:

Time	t_i [min]	0	3	5	10	20	30	43
BSP	r_i [mg]	250	221	184	141	98	80	64

In the second table there are the values of the amount of BSP in the bile:

Time	s_j [min]	0	5	10	15	20	25	30
BSP	e_j [mg]	0	0.2	2.5	6	10.5	15.8	21.7
Time	s_j [min]	35	40	45	50	60	70	80
BSP	e_j [mg]	28	34.8	41.8	49	63.8	78.5	92.7
Time	s_j [min]	90	100	110	120	130	140	150
BSP	e_j [mg]	105.7	117	127.1	136.3	144.5	152.1	159.2

For numerical computations we use cubic splines interpolating these data.

4. Modified quasilinearization method for the inverse problem

We use a modification of the quasilinearization method for determining the unknown parameters characterizing the mathematical models describing the BSP kinetics in the human liver. We describe this method briefly.

Let $Q \subset R^n$ be closed convex set of the variables $x = (x_1, \ldots, x_n)^\top$ and $D \subset R^N$ be closed convex set of the parameters $\alpha = (\alpha_1, \ldots, \alpha_N)^\top$. Let $f : Q \times D \to R^n$ have continuous bounded partial derivatives up to the second order. Consider a nonlinear autonomous system of ordinary differential equations with the initial condition

$$\dot{x} = f(x, \alpha), \quad x(0) = c. \tag{4.1}$$

The aim is to find the unknown parameters α such that the solution of the initial problem (4.1) fits in some sense to the measured data, respectively to the continuous function which approximates these data. In order to avoid considering two different types of vectors we will suppose that the vector α satisfies the differential equation

$$\dot{\alpha} = 0$$

with the initial condition

$$\alpha(0) = \beta.$$

Define a new vector $\mathbf{x}$ by

$$\mathbf{x} = (x, \alpha)^\top = (x_1, \ldots, x_n, \alpha_1, \ldots, \alpha_N)^\top \in R^{n+N},$$

and a vector $\mathbf{c}$ (corresponding to the initial condition) by

$$\mathbf{c} = (c, \beta)^\top = (c_1, \ldots, c_n, \beta_1, \ldots, \beta_N)^\top \in R^{n+N}.$$

The vector $\mathbf{x}(t)$ satisfies the nonlinear differential equation

$$\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x}), \tag{4.2}$$

where $\mathbf{g}(\mathbf{x}) = (f(x, \alpha), \underbrace{0, \ldots, 0}_{N})^\top$, with the initial condition

$$\mathbf{x}(0) = \mathbf{c}. \tag{4.3}$$

Let $\mathbf{x}^{(k)}(t)$ (k–th approximation) be a solution to (4.2) on the interval $[0, T]$ with the initial condition (4.3) for $\beta_1 = \alpha_1^{(k)}, \ldots, \beta_N = \alpha_N^{(k)}$, i.e.

$$\mathbf{x}^{(k)}(0) = (c_1, \ldots, c_n, \alpha_1^{(k)}, \ldots, \alpha_N^{(k)})^\top$$

(the k–th approximation of the solution).

The deviation between this solution and the functions $r(t) = (r_1(t), \ldots, r_n(t))^\top$, $e(t)$ approximating the experimental (measured) values has the form

$$\begin{aligned} S(\mathbf{x}^{(k)}) &= \sum_{l=1}^{n} \Big(\int_0^T (\mathbf{x}_l^{(k)}(t) - r_l(t))^2 \, dt \Big) + \\ &\quad + \int_0^T \Big((\gamma + \sum_{l=1}^{n} \gamma_l \mathbf{x}_l^{(k)}(t)) - e(t) \Big)^2 \, dt, \end{aligned} \tag{4.4}$$

where γ, γ_l are real constants.

We would like to find a new vector of parameters $\beta = \alpha^{(k+1)}$ so that

$$S(\mathbf{x}^{(k+1)}) < S(\mathbf{x}^{(k)}). \tag{4.5}$$

The dependence $\mathbf{x}^{(k)}(t)$ on the parameters β ($\beta = \alpha^{(k)}$) is not clear, therefore we approximate $\mathbf{x}^{(k)}(t)$ by the solution $\mathbf{y}^{(k+1)}(t)$ of linearized system

$$\dot{\mathbf{y}}(t) = \mathbf{g}(\mathbf{x}^{(k)}(t)) + \mathbf{J}(\mathbf{x}^{(k)}(t))(\mathbf{y}(t) - \mathbf{x}^{(k)}(t)), \tag{4.6}$$

where $\mathbf{J}(\mathbf{x})$ is the Jacobian matrix of $\mathbf{g}(\mathbf{x})$ with elements

$$\mathbf{J}_{ij} = \frac{\partial \mathbf{g}_i}{\partial \mathbf{x}_j}$$

in the i-th row and j-th column, $i, j = 1, \ldots, n+N$.

The equation (4.6) represents a linear system of $n+N$ differential equations and its general solution $\mathbf{y}(t)$ with

$$\mathbf{y}_l(0) = c_l, \quad l = 1, \ldots, n \tag{4.7}$$

can be expressed in the form

$$\mathbf{y}(t) = \mathbf{y}^{(k+1)}(t) = \mathbf{p}^{(k+1)}(t) + \sum_{j=1}^{N} \beta_j \mathbf{h}^{(j,k+1)}(t). \tag{4.8}$$

The function $\mathbf{p}^{(k+1)}(t)$ is the (particular) solution of the nonhomogeneous equation

$$\dot{\mathbf{p}}(t) = \mathbf{g}(\mathbf{x}^{(k)}(t)) + \mathbf{J}(\mathbf{x}^{(k)}(t))(\mathbf{p}(t) - \mathbf{x}^{(k)}(t)) \tag{4.9}$$

which fulfils the initial condition

$$\mathbf{p}(0) = (c_1, \ldots, c_n, 0, \ldots, 0)^\top.$$

The $(n+N)$–column vectors $\mathbf{h}^{(j,k+1)}(t)$, $j = 1, \ldots, N$, are solutions of the homogeneous system

$$\dot{\mathbf{h}}^{(j,k+1)}(t) = \mathbf{J}(\mathbf{x}^{(k)}(t))\mathbf{h}^{(j,k+1)}(t) \tag{4.10}$$

with

$$\mathbf{h}_i^{(j,k+1)}(0) = \begin{cases} 0, & \text{for } i \neq j+n \\ 1, & \text{for } i = j+n, \ i = 1, \ldots, n+N. \end{cases} \tag{4.11}$$

The equality (4.8) immediately implies that the dependence of $\mathbf{y}^{(k+1)}(t)$ on the parameters β_j, $j = 1, \ldots, N$ is linear. The parameters β_j, $j = 1, \ldots, N$ are free and they can be used for minimizing the function

$$S(\mathbf{y}^{(k+1)}) = S_{k+1}(\beta) = S_{k+1}(\beta_1, \ldots, \beta_N) =$$

$$\sum_{l=1}^{n} \Big(\int_0^T (\mathbf{y}_l^{(k+1)}(t) - r_l(t))^2 \, dt \Big) + \int_0^T (\gamma + \sum_{l=1}^{n} \gamma_l \mathbf{y}_l^{(k+1)}(t) - e(t))^2 \, dt.$$

It is easy to see that the functional $S_{k+1}(\beta)$ is a strictly convex function with a unique point of minimum β^*. Put

$$\alpha^{(k+1)} = \beta^* = (\beta_1^*, \ldots, \beta_N^*)^\top$$

if

$$\|\alpha^{(k+1)} - \alpha^{(k)}\| \leq \zeta_k, \tag{4.12}$$

for arbitrary small $\zeta_k > 0$, and $S(\mathbf{x}^{(k+1)}) < S(\mathbf{x}^{(k)})$, where $\mathbf{x}^{(k+1)}(t)$ is the solution of the equation (4.2) wtih the initial condition

$$\mathbf{x}^{(k+1)}(0) = (c, \alpha^{(k+1)})^\top.$$

Then we can repeat the whole process of evaluation until one of the following conditions is satisfied

I. $S(\mathbf{x}^{(k+1)}) = S(\mathbf{x}^{(k)})$.

II. $S(\mathbf{x}^{(k)}) - S(\mathbf{x}^{(k+1)}) < \varepsilon$, where $\varepsilon > 0$.

If the inverse inequality is fulfiled, i.e. $S(\mathbf{x}^{(k+1)}) > S(\mathbf{x}^{(k)})$, we do not repeat the whole process of computation, but we must start with a better choice of the initial approximation α_1.

If the equality

$$S(\mathbf{x}^{(k+1)}) = S(\mathbf{x}^{(k)}),$$

holds, we get the required values of parameters $\alpha = \alpha^{(k)}$. Noting that the deviation is not altered we finish our computation.

If the inequality (4.5) is fulfiled, but

$$\|\alpha^{(k+1)} - \alpha^{(k)}\| \geq \zeta_k,$$

we have to modify the value of the parameter $\alpha^{(k+1)}$. The modification is based on the following lemma.

Lemma 4.1. *Let $\alpha^{(k)}$ be fixed for given k.*

Then for arbitrary $\zeta_k > 0$ there is a parameter $\alpha^{(k+1)} \in M_k$, where

$$M_k := \{\beta | \beta \in D, S_{k+1}(\beta) \leq S(\mathbf{x}^{(k)})\}$$

is a convex set, such that

$$\|\alpha^{(k+1)} - \alpha^{(k)}\| \leq \zeta_k.$$

We are able to choose ζ_k in Lemma 4.1 so that the sequence $\{\zeta_k\}_{k=1}^{\infty}$ is decreasing, its upper bound is ζ_1 and $\liminf \zeta_k = 0$. Therefore

$$\lim_{k \to \infty} \zeta_k = 0.$$

In addition, we can construct this sequence in such a way that

$$\sum_{k=1}^{\infty} \zeta_k < \infty.$$

Theorem 4.2. *Let $\alpha^{(k)} \in D$, for every $k = 1, 2, \ldots$, where $D \subset R^N$ is closed convex subset. Let the sequence of the parameters $\{\alpha^{(k)}\}_{k=1}^{\infty}$ satisfy the inequality (4.12), for every k, i.e.,*

$$\|\alpha^{(k+1)} - \alpha^{(k)}\| \leq \zeta_k.$$

Let the sequence ζ_k be convergent and decreasing such that

$$\sum_{k=1}^{\infty} \zeta_k = \zeta < \infty.$$

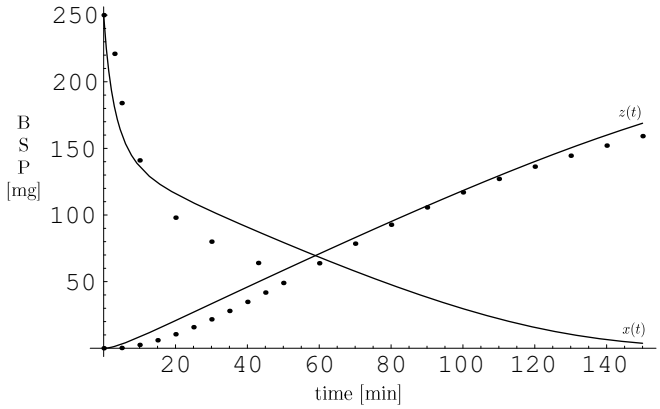
Then $\{\alpha^{(k)}\}_{k=1}^{\infty}$ is a Cauchy sequence.

5. Numerical results

Numerical results concerning the simple mathematical model JLM (2.1) are presented in [7]. For illustration we will present the results for nonlinear system (2.3) with the initial condition (2.2), $I = 250$. Select the initial aproximation

$$\alpha^{(1)} = (K^{(1)}, b_1^{(1)}, b_2^{(1)})^\top = (123, 0.0013, 0.0111)^\top.$$

The corresponding graph consists of components $x(t)$, $z(t)$:



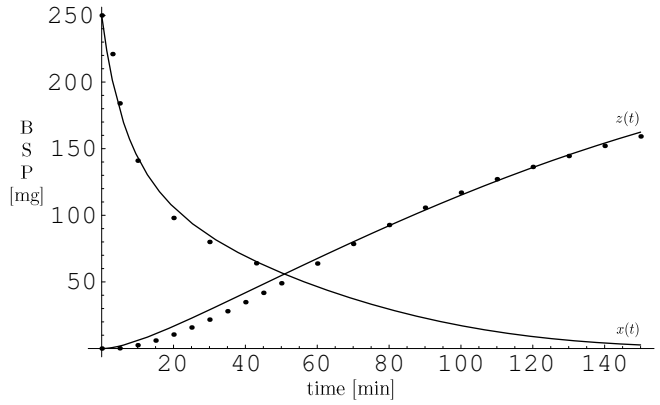
The value of the deviation (4.4) is $S(\mathbf{x}^{(1)}) = 25\,650$. We stopped the computational algorithm after 650 iterations, since the condition

$$S(\mathbf{x}^{(650)}) - S(\mathbf{x}^{(649)}) < \varepsilon = 0.75$$

was fulfiled. The values of parameters are as follows:

$$\begin{aligned} K^{(650)} &= 180.344, \\ b_1^{(650)} &= 0.472971 * 10^{-3}, \\ b_2^{(650)} &= 0.930451 * 10^{-2}. \end{aligned}$$

We obtain the deviation $S(\mathbf{x}^{(651)}) = 4\,286{,}33$, and the corresponding graph



6. Publications concerning the thesis

[1] Čelechovská, L., *A simple mathematical model of the human liver*, Appl. Math. (to appear)[1]

[2] Čelechovská, L., *Convergence of the Quasilinearization method*, Preprint MA 38/2003[2]

[3] Čelechovská, L., *Mathematical Models of BSP Kinetics in the Human Liver*, 3rd International Conference APLIMAT 2004, Bratislava[2]

7. Presentations

[1] 5th Czech-Slovak Conference on Dynamical systems, Praděd, Czech Republic, June 16-23, 2001
Lecture: *A simple mathematical model of the human liver.*

[2] Conference on Differential Equations and their Applications (EQUADIFF 10) Prague, August 2731, 2001.
Poster: *A simple mathematical model of the human liver.*

[3] International Conference on Differential and Difference Equations and their Applications (ICDDEA), Patras, Greece, July 15, 2002
Lecture: *Mathematical model of the human liver and quasilinearization method.*

[4] Biomathematics Euro Summer School, Dynamical Systems in Physiology and Medicine, Urbino, Italy, July 819, 2002
Lecture: *Mathematical models of the human liver.*

[5] Universidad Politécnica de Cartagena, Universidad de Murcia, 28.4-9.5.2003
Lecture: *Identification of the parameters of the mathematical models of the human liver.*

[6] 7th Czech-Slovak Conference on Dynamical systems, Praděd, Czech Republic, September 6-13, 2003
Lecture: *Verification of the mathematical model of the human liver.*

[7] 3rd International Conference Aplimat, Bratislava, Slovak Republic, February 3 - 6, 2004.
Lecture: *Mathematical models of BSP kinetics in the human liver.*

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[1]The research was supported, in part, by the Grant Agency of Czech Republic, grant No. 201/00/0859 and the Czech Ministry of Education, contract No. MSM 192400002.

[2]The research was supported, in part, by the Grant Agency of Czech Republic, grant No. 201/03/1153 and the Czech Ministry of Education, project MSM 192400002.

[7] Čelechovská, L., *A simple mathematical model of the human liver*, Appl. Math. (to appear)
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