Applications of Mathematics

Lenka Čelechovská

A simple mathematical model of the human liver

Applications of Mathematics, Vol. 49 (2004), No. 3, 227–246

Persistent URL: http://dml.cz/dmlcz/133895

49 (2004) APPLICATIONS OF MATHEMATICS No. 3, 227–246

A SIMPLE MATHEMATICAL MODEL OF THE HUMAN LIVER

LENKA ČELECHOVSKÁ, Opava

(Received March 4, 2002)

Abstract. The parameter estimation problem for a continuous dynamical system is a difficult one. In this paper we study a simple mathematical model of the liver. For the parameter identification we use the observed clinical data obtained by the BSP test. Bellman's quasilinearization method and its modifications are applied.

Keywords: identification of parameters, quasilinearization method

MSC 2000: 34B60, 92C50

1. THE PHYSIOLOGICAL PROBLEM AND A SIMPLE MATHEMATICAL MODEL

This note is devoted to the problem of mathematical modelling of the liver functions. The mathematics concerning the models should be done in such a way that data given by clinical experiments on humans would give relevant information on the status of an individual. Let us shortly describe the basic procedure for obtaining data.

Bromsulphthalein (BSP) is a colouring matter, which is injected into the blood. The liver is the only organ which takes BSP and secretes BSP directly into the bile, i.e. we can assume that the BSP is not taken up by any other organ in the body. The level of BSP in the blood is measured at different times t. This procedure is relatively simple from the practical point of view; it gives a finite sequence of values showing the more or less rapid decrease of BSP in the blood and is used for investigation of the function of the liver.

Denote by x, y, z the amount of BSP in the blood, in the liver and in the bile at time t, respectively.

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 in the form of the

system of linear ordinary differential equations

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= -ax + by, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= ax - (b+d)y, \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= dy. \end{aligned} \tag{1.1}$$

The constants a, b, d are the rates of transfer and they are unknown. In this way the mathematical model describing the liver function was presented in [5].

Suppose that there is a "single injection", in which some quantity $I > 0$ of BSP is injected into the blood at once. This leads to initial conditions

$$x(0) = I, \quad y(0) = 0, \quad z(0) = 0, \quad I > 0 \tag{1.2}$$

for the system (1.1). The constants a, b, d characterize the system and in some sense they should characterize the clinical status of the human. How reliable information of this kind is, is not very clear at this moment.

Let us note that the quantity $z(t)$ can be looked upon as the efflux of BSP from the system which is investigated and that from the viewpoint of the dynamics of the process it plays a role which is not very essential. The value of $z(t)$ can be reconstructed from the knowledge of $x(t)$ and $y(t)$. Indeed, looking at the system we can see immediately, by adding the equations in (1.1), that

$$\frac{\mathrm{d}(x+y+z)}{\mathrm{d}t} = 0$$

and

$$x(0) + y(0) + z(0) = I.$$

This means that

$$x(t) + y(t) + z(t) = I \tag{1.3}$$

for all $t \geqslant 0$ and

$$z(t) = I - x(t) - y(t)$$

for $t \geqslant 0$.

Therefore it is enough to consider the lower dimensional system of linear ordinary differential equations

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= -ax + by, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= ax - (b+d)y \end{aligned} \tag{1.4}$$

subject to the initial conditions

$$x(0) = I, \quad y(0) = 0, \quad I > 0. \tag{1.5}$$

Note that the constants a, b, d occuring in the system (1.1) have to be positive since they represent the rates of decay of BSP from the blood and the liver. Therefore we assume in the sequel that

$$a > 0, \quad b > 0, \quad d > 0.$$

The clinical test described above gives information on the numerical values of $x(t)$ for some finite number of instants t.

Assume that the function x is known for all t in an interval $[0, T]$, $T > 0$ and investigate the problem how much information about the system, i.e. about the constants a, b, d, is contained in this knowledge.

Let us suppose another system is given and that it has the same structure as (1.4) but the coefficients are different:

$$\begin{aligned} \frac{\mathrm{d}X}{\mathrm{d}t} &= -AX + BY, \\ \frac{\mathrm{d}Y}{\mathrm{d}t} &= AX - (B + D)Y. \end{aligned} \tag{1.6}$$

Assume that for the first component $X(t)$ of the solution we have

$$x(t) = X(t) \tag{1.7}$$

if $t \in [0, T]$. Then

$$\dot{x}(t) = \dot{X}(t)$$

for $t \in [0, T]$, consequently

$$-ax(t) + by(t) = -AX(t) + BY(t)$$

and

$$AX(t) - ax(t) = (A - a)x(t) = BY(t) - by(t).$$

Since $Y(0) = y(0) = 0$ and $x(0) = I > 0$ we obtain

$$A = a \tag{1.8}$$

and

$$y(t) = \frac{B}{b} Y(t).$$

Using the equality

$$\dot{y}(t) + (b+d)y(t) = ax(t) = AX(t) = \dot{Y}(t) + (B+D)Y(t)$$

and (1.8) we get

$$\dot{y}(t) - \dot{Y}(t) = \dot{Y}(t)\Big(\frac{B}{b} - 1\Big) = Y(t)\Big(D - \frac{dB}{b}\Big).$$

Since $Y(0) = 0$ and $\dot{Y}(0) = AI > 0$ we obtain

$$b = B$$

and consequently $d = D$.

This shows that in our case the system is uniquely determined. This means that the coefficients in (1.4) are determined uniquely. Let us mention that if we know the efflux $z(t)$ on the interval $[0,T]$, then by the relation (1.3) the values of $y(t)$ are also known on $[0,T]$ and the knowledge of $z(t)$ leads also to the unicity of the mathematical model.

Of course this mathematical fact leads to technical problems. The amounts of BSP in the bile can be measured only in the case when the patient is after a cholecystectomy and a drain takes out all the bile from the body. The efflux is known in this case and there is a theoretical possibility to identify the system, i.e. to determine the coefficients a, b and d.

2. Some properties of the system

The process of development of the amounts of BSP in the blood and liver is described by the relatively simple linear model of ODE's presented in the previous section.

It is easy to see that the equilibrium points of the system (1.4) are given by the solutions of the algebraic system

$$\begin{aligned} -ax + by &= 0, \\ ax - (b+d)y &= 0. \end{aligned}$$

It can be seen easily that there is only one equilibrium point $P = (0,0)$ under the assumption $a > 0$, $b > 0$, $d > 0$.

Let us investigate the stability of the system (1.4) at the point P. The matrix of the system (1.4) is

$$A = \begin{pmatrix} -a & b \\ a & -b-d \end{pmatrix}$$

and the characteristic values of this matrix, given by the algebraic equation

$$\det(A - \lambda E) = \lambda^2 + \lambda(a + b + d) + ad = 0,$$

are

$$\lambda_{1,2} = \frac{-(a + b + d) \pm \sqrt{(a + b + d)^2 - 4ad}}{2}.$$

If a, b and d are positive, then

$$|a + b + d|^2 > (a + b + d)^2 - 4ad \geqslant 0,$$

and so the characteristic values $\lambda_{1,2}$ are negative, which means that the solution $x(t) = 0$, $y(t) = 0$ corresponding to the equilibrium P of (1.4) is globally asymptoticaly stable.

Besides these basic qualitative properties of a solution to the system (1.4) we can express explicitly the solution to the initial value problem (1.4), (1.5) in the form

$$x(t) = \frac{(a - b - d)I}{2\sqrt{(a + b + d)^2 - 4ad}}\left(e^{\lambda_2 t} - e^{\lambda_1 t}\right) + \frac{I}{2}\left(e^{\lambda_1 t} + e^{\lambda_2 t}\right), \tag{2.1}$$

$$y(t) = -\frac{a\left(-e^{\lambda_1 t} + e^{\lambda_2 t}\right)I}{\sqrt{(a + b + d)^2 - 4ad}}. \tag{2.2}$$

3. Clinical data

The structure of data describing the decay of BSP in the blood is given by a finite set of times $t_1, t_2, \ldots, t_L$ at which the amounts $r_1, r_2, \ldots, r_L$ of BSP are measured. The first time is $t_1 = 0$ and the corresponding value of r_1 is the value corresponding to the injection I administered to the patient.

At the finite set of times $s_1, s_2, \ldots, s_M$ the amounts of the efflux $e_1, e_2, \ldots, e_M$ of BSP into the bile are measured.

Note that this last measurement was possible only in the case that a drain was inserted into the channel connecting the liver with the gall-bladder. As it was mentioned above a cholecystectomy makes this possible in some cases.

Let us present a typical set of clinical data. The measured values of the amount of BSP in the blood are given in the following table.[1]

t_i	0	3	5	10	20	30	43
r_i	250	221	184	141	98	80	64

[1] All the data presented in this work were obtained by Prof. Evžen Hrnčíř in 1985. New technologies today can maybe give similar data sets without the invasive technology of a cholecystectomy.

The measured efflux into the bile is presented in the following table.

s_j	5	10	15	20	25	30	35	40	45	50
e_j	0.2	2.5	6	10.5	15.8	21.7	28	34.8	41.8	49

s_j	60	70	80	90	100	110	120	130	140	150
e_j	63.8	78.5	92.7	105.7	117	127.1	136.3	144.5	152.1	159.2

The aim is to find the coefficients a, b and d of the system of ordinary differential equations (1.4) subject to the initial conditions (1.5) which in some sense correspond to the measured data of this type. The concept of correspondence will be described bellow.

Since by (2.1), (2.2) the exact solution to (1.4), (1.5) is known, the deviation of the exact solution from the observed data can be expressed in the form

$$S = \sum_{i=1}^{L}(x(t_i) - r_i)^2 + \sum_{j=1}^{M}(z(s_j) - e_j)^2,$$

where $z(t)$ is the efflux at the time t given by (1.3).

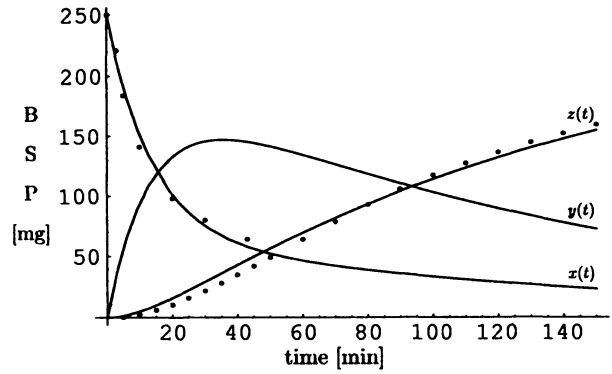
So we have in fact

$$S = \sum_{i=1}^{L}(x(t_i) - r_i)^2 + \sum_{j=1}^{M}((I - x(s_j) - y(s_j)) - e_j)^2. \tag{3.1}$$

The nonnegative value of the deviation S depends of course on the parameters a, b and d of the system (1.4) and this value has to be minimized with respect to a, b and d.

It is clear that it is a difficult task to find the minimum of S and that numerical methods have to be used there. The Mathematica program package can be used for concrete computations. Using the `FindMinimum` command of Mathematica gives for the presented set of clinical data the approximate result that the function S attains its minimum $S = 862.546$ at $a = 0.0547241$, $b = 0.0152577$, $d = 0.00939036$.

Representing this result graphically we obtain the picture which shows that the values of x and z for the exact solution to the system (1.4), (1.5) are close to the measured clinical values indicated by dots in the picture.



4. Quasilinearization method

The main method in system identification is the quasilinearization technique which will be described in this part. This method was first used by R. Bellman [1]. The method consists in the construction of a sequence of functions $\mathbf{x}^n(t)$ which converges to the solution of the differential equation in such a way that the deviation S goes to its (local) minimum. The general formulation of this method for system identification is described in detail in [4]. We must emphasize that good convergence results can be achieved when we have a good initial approximation $\mathbf{x}^1(t)$.

We shall work in the finite-dimensional space $\mathbb{R}^m$. The norm $\|x\|$ of a vector $x = (x_1, \ldots, x_m)^\top$ is[2]

$$\|x\| := \max_{i=1,\ldots,m} |x_i|.$$

If $A = (a_{ij})$, $i, j = 1, \ldots, m$ is an $m \times m$-matrix, then $\|A\|$ denotes the (operator) norm corresponding to the given norm of m-vectors. For the norm of an m-vector presented above the norm of a matrix is given by

$$\|A\| := \max_{i=1,\ldots,m} \sum_{j=1}^{m} |a_{ij}|.$$

4.1. The general formulation

Consider a nonlinear autonomous system of ordinary differential equations

$$\dot{x}(t) = f(x(t), \alpha), \tag{4.1}$$

where $x(t) = (x_1(t), \ldots, x_n(t))^\top$ is an n-dimensional vector, $\alpha = (\alpha_1, \ldots, \alpha_N)^\top$ is an N-dimensional vector of parameters and $f\colon \mathbb{R}^n \times \mathbb{R}^N \to \mathbb{R}^n$ is a continuous function

[2] By the symbol $^\top$ we denote the transposition of a matrix, e.g. $(x_1, \ldots, x_m)^\top$ is the column vector with components $x_1, \ldots, x_m$.

of (x, α) having continuous bounded partial derivatives with respect to x and α for all (x, α) in the region of interest.

For the system (4.1) consider the initial value problem

$$x_j(0) = c_j, \quad j = 1, \ldots, n, \tag{4.2}$$

with known values of c_j, $j = 1, \ldots, n$. The N parameters α are arbitrary.

Consider the constant vector α to be a function of time that satisfies the differential equation

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

Define $\mathbf{x}(t)$ as an $(n + N)$-dimensional vector and a vector $\mathbf{c}$ (corresponding to the initial conditions) as follows

$$\mathbf{x}(t) = (x_1(t), \ldots, x_n(t), \alpha_1(t), \ldots, \alpha_N(t))^\top,$$
$$\mathbf{c} = (c_1, \ldots, c_n, \nu_1, \ldots, \nu_N)^\top.$$

Assume that $\mathbf{g}(\mathbf{x}(t)) = (f(x(t), \alpha), \underbrace{0, \ldots, 0}_{N})^\top$.

If $x(t)$ is a solution of the system (4.1) with (4.2) and with $\alpha_j = \nu_j$, $j = 1, \ldots, N$, then the vector $\mathbf{x}(t) = (x(t), \alpha(t))^\top$ is a solution of the initial value problem

$$\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x}), \quad \mathbf{x}(0) = \mathbf{c}, \tag{4.3}$$

and, conversely, if $\mathbf{x}(t)$ is a solution of (4.3) then the first n components of this solution represent a solution of (4.1) with (4.2) and with $\alpha_j = \nu_j$, $j = 1, \ldots, N$.

Given a fixed solution $\widetilde{\mathbf{x}}(t)$ of the differential equation (4.3), the system (4.3) can be linearized around this solution.

The linearized system has the form

$$\dot{\mathbf{y}} = \mathbf{g}(\widetilde{\mathbf{x}}) + \mathbf{J}(\widetilde{\mathbf{x}})(\mathbf{y} - \widetilde{\mathbf{x}}), \tag{4.4}$$

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

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

in the ith row and jth column, $i, j = 1, \ldots, n + N$, and we use it for $\mathbf{x} = \widetilde{\mathbf{x}}(t)$ in the equation (4.4).

The equation (4.4) represents a linear system of $n + N$ differential equations for $\mathbf{y}$ and its solution $\mathbf{y}(t)$ for which $\mathbf{y}_j(0) = c_j$, $j = 1, \ldots, n$, can be represented in the form

$$\mathbf{y}(t) = \mathbf{p}(t) + \sum_{j=1}^{N} \beta_j \mathbf{h}^{(j)}(t) \tag{4.5}$$

where $\mathbf{p}(t)$ is the (particular) solution of

$$\dot{\mathbf{p}} = \mathbf{g}(\tilde{\mathbf{x}}) + \mathbf{J}(\tilde{\mathbf{x}})(\mathbf{p} - \tilde{\mathbf{x}}) \tag{4.6}$$

with the initial condition

$$\mathbf{p}_j(0) = c_j, \quad j = 1, \dots, n, \quad \mathbf{p}_{l+n}(0) = 0, \quad l = 1, \dots, N,$$

and $\mathbf{h}^{(j)}(t)$, $j = 1, \dots, N$, are solutions of the homogeneous system

$$\dot{\mathbf{h}}^{(j)} = \mathbf{J}(\tilde{\mathbf{x}})\mathbf{h}^{(j)} \tag{4.7}$$

with $\mathbf{h}_i^{(j)}(0) = 0$ for $i \neq j + n$, $i = 1, \dots, n + N$, and $\mathbf{h}_{j+n}^{(j)}(0) = 1$.

Further we prove the following lemma.

Lemma 4.1. *Assume that $\tilde{\mathbf{x}}(t)$ is a solution of the initial value problem* (4.3) *and that $\mathbf{y}(t)$ is a solution of the equation* (4.4) *in the form* (4.5) *with the initial conditions*

$$\mathbf{y}_j(0) = \begin{cases} c_j, & \text{for } j = 1, \dots, n \\ \beta_{j-n}, & \text{for } j = n+1, \dots, n+N. \end{cases} \tag{4.8}$$

If, moreover, $\nu_i = \beta_i$, $i = 1, \dots, N$, then

$$\mathbf{y}(t) = \tilde{\mathbf{x}}(t)$$

for $t \geqslant 0$, i.e. the solution of the linearized equation (4.4) *coincides with the solution $\tilde{\mathbf{x}}(t)$ of* (4.3) *in this case.*

Proof. For the difference $\mathbf{y}(t) - \tilde{\mathbf{x}}(t)$ we have the following differential equation

$$\frac{\mathrm{d}}{\mathrm{d}t}(\mathbf{y} - \tilde{\mathbf{x}}) = \mathbf{g}(\tilde{\mathbf{x}}) + \mathbf{J}(\tilde{\mathbf{x}})(\mathbf{y} - \tilde{\mathbf{x}}) - \mathbf{g}(\tilde{\mathbf{x}}) = \mathbf{J}(\tilde{\mathbf{x}})(\mathbf{y} - \tilde{\mathbf{x}}).$$

Integrating this equation from 0 to t we have

$$\mathbf{y}(t) - \tilde{\mathbf{x}}(t) = \mathbf{y}(0) - \tilde{\mathbf{x}}(0) + \int_0^t \mathbf{J}(\tilde{\mathbf{x}}(s))(\mathbf{y}(s) - \tilde{\mathbf{x}}(s))\,\mathrm{d}s$$

and

$$\begin{aligned} \|\mathbf{y}(t) - \tilde{\mathbf{x}}(t)\| &\leqslant \|\mathbf{y}(0) - \tilde{\mathbf{x}}(0)\| + \int_0^t \|\mathbf{J}(\tilde{\mathbf{x}}(s))\|\|\mathbf{y}(s) - \tilde{\mathbf{x}}(s)\|\,\mathrm{d}s \\ &= \|\mathbf{y}(0) - \mathbf{c}\| + \int_0^t \|\mathbf{J}(\tilde{\mathbf{x}}(s))\|\|\mathbf{y}(s) - \tilde{\mathbf{x}}(s)\|\,\mathrm{d}s. \end{aligned}$$

By the Gronwall lemma we obtain

$$\|\mathbf{y}(t) - \tilde{\mathbf{x}}(t)\| \leqslant \|\mathbf{y}(0) - \mathbf{c}\| \cdot \exp\left(\int_0^t \|\mathbf{J}(\tilde{\mathbf{x}}(s))\|\,\mathrm{d}s\right).$$

Since $\mathbf{y}(0) = \mathbf{c}$, we have $\mathbf{y}(t) = \tilde{\mathbf{x}}(t)$ for $t \geqslant 0$. □

From (4.5) we can see immediately that the dependence of $\mathbf{y}(t)$ 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 a certain expression S which measures the deviation of the solution $\mathbf{y}(t)$ to (4.4) from some observed state.

The function S be of the following form

$$\begin{aligned} S(\mathbf{y}) &= S(\beta_1, \ldots, \beta_N) \\ &= \sum_{l=1}^{n} \sum_{i=1}^{L_l} \left(\mathbf{y}_l(t_i^l) - r_i^l\right)^2 + \sum_{j=1}^{M} \left(\left(\gamma + \sum_{l=1}^{n} \gamma_l \mathbf{y}_l(s_j) \right) - e_j \right)^2 \end{aligned}$$

where γ, γ_l, $l = 1, \ldots, n$, are some constants, t_i^l and s_j are some instants of time at which the experimental data r_i^l and e_j are known for the components of the solutions or some of their linear combinations.

In view of (4.5), we observe that $S(\mathbf{y})$ is a quadratic form in the variables $\beta_1, \ldots, \beta_N$. If this quadratic form is well behaved, the necessary conditions for finding its local minimum are given by

$$\frac{\partial S}{\partial \beta_j} = 0, \quad j = 1, \ldots, N, \tag{4.9}$$

which is a linear system of N algebraic equations for N unknown variables $\beta_1, \ldots, \beta_N$. Denote $\beta_1^*, \ldots, \beta_N^*$ the solution of this system.[3]

In any case putting $\mathbf{c}^* = (c_1, \ldots, c_n, \beta_1^*, \ldots, \beta_N^*)^\top$ we have new initial conditions and the procedure can be repeated by finding a solution $\mathbf{x}^*(t)$ of the differential equation $\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x})$ with the new initial conditions $\mathbf{x}(0) = \mathbf{c}^*$, linearizing the equation around $\mathbf{x}^*(t)$ and computing new initial values as above.

In this way in fact an iterative procedure is given which consists in finding a sequence of parameters $\beta_1^{(k)}, \ldots, \beta_N^{(k)}$, $k = 1, 2, \ldots$, for which the sequence $S\left(\beta_1^{(k)}, \ldots, \beta_N^{(k)}\right)$ decreases to some local minimum of S.

From the practical point of view the iterative procedure has to be repeated until

$$\beta_j^{(k+1)} = \beta_j^{(k)}, \quad j = 1, \ldots, N \tag{4.10}$$

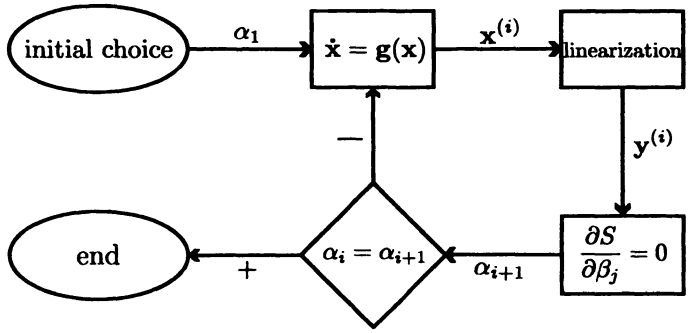
or

$$\left|\beta_j^{(k+1)} - \beta_j^{(k)}\right| < \varepsilon, \quad j = 1, \ldots, N \tag{4.11}$$

with some sufficiently small $\varepsilon > 0$.

[3] Using contemporary computational tools, e.g. the `FindMinimum` command in the Mathematica package, another way of finding the values $\beta_1^*, \ldots, \beta_N^*$ which minimize $S(\mathbf{y}) = S(\beta_1, \ldots, \beta_N)$ can be found.

Remark 4.2. For the sake of clarity, we summarize the quasilinearization method in a flow diagram.



4.2. Application of the quasilinearization method

We apply the general quasilinearization method described above to the system (1.4). The problem (1.4) subject to the initial conditions (1.5) in fact corresponds to (4.1) with $\alpha = (a, b, d)^\top$, $f((x, y), \alpha) = (-ax + by, ax - (b + d)y)^\top$, and the initial condition (4.2) with $c = (I, 0)$; we have $n = 2$, $N = 3$ in this case.

We set

$$\mathbf{x} = (x, y, a, b, d)^\top.$$

The initial value problem (4.3) takes the form

$$\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x}), \tag{4.12}$$

$$\mathbf{x}(0) = \mathbf{c} = (I, 0, \alpha)^\top \tag{4.13}$$

where

$$\mathbf{g}(\mathbf{x}) = (-ax + by, ax - (b + d)y, 0, 0, 0)^\top. \tag{4.14}$$

The Jacobian matrix $\mathbf{J}(\mathbf{x})$ corresponding to this $\mathbf{g}(\mathbf{x})$ is given by

$$\mathbf{J}(\mathbf{x}) = \begin{pmatrix} -a & b & -x & y & 0 \\ a & -b-d & x & -y & -y \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Let us note that the function $\mathbf{g}\colon \mathbb{R}^5 \longrightarrow \mathbb{R}^5$ given by (4.14) is continuously differentiable. Therefore the solutions of (4.12) are uniquely determined by the initial

conditions. The last three components of any solution to (4.12) are constant and equal to the triple $\alpha = (a, b, d)$.

Hence the differential equation (4.12) has nice properties; in particular, the solutions depend continuosly on the initial conditions. Taking into account Section 2 and the fact that the only equlibrium $P = (0, 0)$ of the system (1.4) is globally asymptotically stable, we can see easily that for all solutions $\mathbf{x}(t)$, $t \geqslant 0$ of (4.12) with $\mathbf{x}(0) = (I, 0, a, b, d)$ we have

$$\mathbf{x}(t) \in [0, I] \times [0, I] \times [0, A] \times [0, B] \times [0, D] \subset \mathbb{R}^5$$

provided $0 < a \leqslant A$, $0 < b \leqslant B$, $0 < d \leqslant D$, i.e. these solutions are bounded in the future.

Using this fact we also obtain the boundedness of $\|\mathbf{J}(\mathbf{x}(t))\|$ for all $t \geqslant 0$, where $\mathbf{x}(t)$ is a solution of (4.12), if $0 < a \leqslant A$, $0 < b \leqslant B$, $0 < d \leqslant D$.

Given a solution $\widetilde{\mathbf{x}}(t)$ of (4.12), (4.13) for some choice $\alpha = (\widetilde{a}, \widetilde{b}, \widetilde{d})^\top$, or in other words a solution $(\widetilde{x}, \widetilde{y})^\top$ of (1.4) with these values of the parameters, the linearized system (4.4) around the solution $\widetilde{\mathbf{x}}(t)$ assumes the form

$$\dot{\mathbf{y}} = \mathbf{g}(\widetilde{\mathbf{x}}) + \mathbf{J}(\widetilde{\mathbf{x}})(\mathbf{y} - \widetilde{\mathbf{x}}), \tag{4.15}$$

where $\mathbf{y}(t) = (y_1(t), \ldots, y_5(t))^\top$. The initial conditions for the first two components are fixed as $y_1(0) = I$, $y_2(0) = 0$, while the initial conditions for $y_3(0)$, $y_4(0)$, $y_5(0)$ are free.

Writing this system componentwise we obtain after a simplification the system

$$\begin{aligned}
\dot{y_1} &= -\widetilde{a}y_1 + \widetilde{b}y_2 - \widetilde{x}(y_3 - \widetilde{a}) + \widetilde{y}(y_4 - \widetilde{b}),\\
\dot{y_2} &= \widetilde{a}y_1 - (\widetilde{b} + \widetilde{d})y_2 + \widetilde{x}(y_3 - \widetilde{a}) - \widetilde{y}(y_4 - \widetilde{b}) - \widetilde{y}(y_5 - \widetilde{d}),\\
\dot{y_3} &= 0, \quad \dot{y_4} = 0, \quad \dot{y_5} = 0.
\end{aligned}$$

The general solution of this problem can be expressed in the form (4.5), i.e.

$$\mathbf{y}(t) = \mathbf{p}(t) + \sum_{j=1}^{3} \beta_j \mathbf{h}^{(j)}(t) \tag{4.16}$$

where the components $p_1(t), \ldots, p_5(t)$ of $\mathbf{p}(t)$ satisfy

$$\begin{aligned}
\dot{p_1} &= -\widetilde{a}p_1 + \widetilde{b}p_2 - \widetilde{x}(p_3 - \widetilde{a}) + \widetilde{y}(p_4 - \widetilde{b}),\\
\dot{p_2} &= \widetilde{a}p_1 - (\widetilde{b} + \widetilde{d})p_2 + \widetilde{x}(p_3 - \widetilde{a}) - \widetilde{y}(p_4 - \widetilde{b}) - \widetilde{y}(p_5 - \widetilde{d}),\\
\dot{p_3} &= 0, \quad \dot{p_4} = 0 \quad \dot{p_5} = 0
\end{aligned} \tag{4.17}$$

with

$$p(0) = (I, 0, 0, 0, 0), \tag{4.18}$$

and for $\mathbf{h}^{(j)}(t)$, $j = 1, 2, 3$ we have for their components $h_1^{(j)}(t), \ldots, h_5^{(j)}(t)$ the equations

$$\begin{aligned} \dot{h_1^{(j)}} &= -\tilde{a}h_1^{(j)} + \tilde{b}h_2^{(j)} - \tilde{x}h_3^{(j)} + \tilde{y}h_4^{(j)}, \\ \dot{h_2^{(j)}} &= \tilde{a}h_1^{(j)} - (\tilde{b} + \tilde{d})h_2^{(j)} + \tilde{x}h_3^{(j)} - \tilde{y}h_4^{(j)} - \tilde{y}h_5^{(j)}, \\ \dot{h_3^{(j)}} &= 0, \quad \dot{h_4^{(j)}} = 0, \quad \dot{h_5^{(j)}} = 0 \end{aligned} \tag{4.19}$$

and the initial conditions

$$\begin{aligned} h^{(1)}(0) &= (0, 0, 1, 0, 0)^\top, \\ h^{(2)}(0) &= (0, 0, 0, 1, 0)^\top, \\ h^{(3)}(0) &= (0, 0, 0, 0, 1)^\top. \end{aligned} \tag{4.20}$$

Using the deviation given by (3.1) in the part concerning the clinical data we write

$$\begin{aligned} S(\mathbf{y}) = S(\beta_1, \beta_2, \beta_3) &= \sum_{i=1}^{L} (y_1(t_i) - r_i)^2 \\ &+ \sum_{j=1}^{M} \big((I - y_1(s_j) - y_2(s_j)) - e_j\big)^2. \end{aligned} \tag{4.21}$$

In view of (4.16), this expression is clearly a quadratic form in β_1, β_2, β_3.

Now we can describe the iterative procedure coming from the quasilinearization method.

Let an initial choice $\alpha_1 = (a_1, b_1, d_1)$ of the parameters be given and let $\mathbf{x}^{(1)}(t)$ be the solution of (4.12) defined for $t \geqslant 0$ with the initial condition

$$\mathbf{x}^{(1)}(0) = (I, 0, a_1, b_1, d_1)^\top.$$

Linearizing (4.12) around $\mathbf{x}^{(1)}$ we get the equation

$$\dot{\mathbf{y}} = \mathbf{g}\big(\mathbf{x}^{(1)}\big) + \mathbf{J}\big(\mathbf{x}^{(1)}\big)\big(\mathbf{y} - \mathbf{x}^{(1)}\big), \tag{4.22}$$

and its solution can be expressed in the form (4.16) where $\mathbf{p}(t)$ and $\mathbf{h}^{(j)}(t)$ are given by the systems (4.17) and (4.19) with initial conditions given by (4.18) and (4.20), respectively, with $\tilde{a} = a_1$, $\tilde{b} = b_1$, $\tilde{d} = d_1$. Using this form of a solution of the linearized equation (4.22) we consider the function $S(y) = S(\beta_1, \beta_2, \beta_3)$ given by (4.21)

and we find its (local) minimum (using some computational or mathematical tool), i.e. a point (a_2, b_2, d_2) at which $S(a_2, b_2, d_2) \leqslant S(a_1, b_1, d_1)$.

Note that by the considerations in the part describing the general form of quasi-linearization (see Lemma 4.1) we have $\mathbf{y}(t) = \mathbf{x}^{(1)}(t)$ if $\beta_1 = a_1$, $\beta_2 = b_1$, $\beta_3 = d_1$ and $S(a_1, b_1, d_1) = S(\mathbf{x}^{(1)})$ is the deviation of $\mathbf{x}^{(1)}(t)$.

Now the iterations are produced as follows.

Given $\alpha_k = (a_k, b_k, d_k)^\top$ let $\mathbf{x}^{(k)}(t)$ be the unique solution of (4.12) given for $t \geqslant 0$ by the initial condition

$$\mathbf{x}^{(k)}(0) = (I, 0, a_k, b_k, d_k)^\top$$

and consider the linearization

$$\dot{\mathbf{y}} = \mathbf{g}\big(\mathbf{x}^{(k)}\big) + \mathbf{J}\big(\mathbf{x}^{(k)}\big)\big(\mathbf{y} - \mathbf{x}^{(k)}\big).$$

We express its solution in the form (4.16) where $\mathbf{p}(t)$ and $\mathbf{h}^{(j)}(t)$ are again given by the systems (4.17) and (4.19) with initial conditions given by (4.18) and (4.20), respectively, with $\widetilde{a} = a_k$, $\widetilde{b} = b_k$, $\widetilde{d} = d_k$, and we look for the (local) minimum of $S(\mathbf{y}) = S(\beta_1, \beta_2, \beta_3)$ to get $\alpha_{k+1} = (a_{k+1}, b_{k+1}, d_{k+1})$ for which $S(a_{k+1}, b_{k+1}, d_{k+1}) \leqslant S(a_k, b_k, d_k)$. We assume that $\mathbf{x}^{(k+1)}(t)$ is the solution of (4.12) for $t \geqslant 0$ with the initial condition $\mathbf{x}^{(k+1)}(0) = (I, 0, a_{k+1}, b_{k+1}, d_{k+1})^\top$.

This iterative procedure leads to a sequence $\mathbf{x}^{(k)}(t) = \big(x^{(k)}(t), y^{(k)}(t), \alpha_k\big)$, where $\alpha_k = (a_k, b_k, d_k)$ is the sequence of parameters.

For a given function $\mathbf{x}(t) = (x(t), y(t), a(t), b(t), d(t))$, $t \in [0, T]$ denote

$$S(\mathbf{x}) = \sum_{i=1}^{L} (x(t_i) - r_i)^2 + \sum_{j=1}^{M} \big((I - x(s_j) - y(s_j)) - e_j\big)^2 \tag{4.23}$$

its deviation from the measured values r_i and e_j.

Let us denote $\mathbf{u} := (x, y, a, b, d)^\top$ and $\mathbf{v} := (\xi, \zeta, \chi, \psi, \omega)^\top$. Then

$$\begin{aligned}\mathbf{R} &:= \mathbf{g}(\mathbf{u}) - \mathbf{g}(\mathbf{v}) - \mathbf{J}(\mathbf{u})(\mathbf{u} - \mathbf{v}) \\ &= \big((x - \xi)(a - \chi) + (y - \zeta)(\psi - b), \\ &\quad (x - \xi)(\chi - a) + (y - \zeta)(b - \psi) + (y - \zeta)(d - \omega), 0, 0, 0\big)^\top\end{aligned}$$

and using the above mentioned norm of a vector we have

$$\begin{aligned}\|\mathbf{R}\| &= \max\big(|(x - \xi)(a - \chi) + (y - \zeta)(\psi - b)|, \\ &\qquad |(x - \xi)(\chi - a) + (y - \zeta)(b - \psi) + (y - \zeta)(d - \omega)|\big) \\ &\leqslant 3\|\mathbf{u} - \mathbf{v}\|^2.\end{aligned} \tag{4.24}$$

Lemma 4.3. *Assume that $T > 0$ is given. Let $\big(\mathbf{x}^{(l)}(t)\big)_{l=1}^{\infty}$ be a sequence of solutions of the equation (4.12) with initial conditions $\mathbf{x}^{(l)}(0) = (I, 0, a_l, b_l, d_l)^{\top}$ which uniformly converges on the interval $[0, T]$.*

Then for every $\varepsilon > 0$ there is a $k_0 \in \mathbb{N}$ such that for every $k_1, k_2 \geqslant k_0$ we have

$$\big\|\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big\| < \varepsilon, \quad t \in [0, T],$$

and putting

$$\mathbf{W}(t) = \mathbf{g}\big(\mathbf{x}^{(k_1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k_2)}(t)\big) - \mathbf{J}\big(\mathbf{x}^{(k_1)}(t)\big)\big(\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big)$$

we also have

$$\int_0^T \|\mathbf{W}(t)\| \, \mathrm{d}t < 3\varepsilon^2 T. \tag{4.25}$$

Proof. The first statement is the Bolzano-Cauchy condition for uniform convergence. Using this and (4.24) with $\mathbf{R} = \mathbf{W}(t)$ we have for $k_1, k_2 \geqslant k_0$

$$\begin{aligned} \int_0^s \big\|\mathbf{g}\big(\mathbf{x}^{(k_1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k_2)}(t)\big) - \mathbf{J}\big(\mathbf{x}^{(k_1)}(t)\big)\big(\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big)\big\| \, \mathrm{d}t \\ \leqslant \int_0^s \big\|\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big\|^2 \, \mathrm{d}t < 3\varepsilon^2 s \end{aligned} \tag{4.26}$$

and (4.25) clearly holds. □

Lemma 4.4. *Assume that $T > 0$ is given. Let $(a_l, b_l, d_l)^{\top}$, $l \in \mathbb{N}$, be a sequence of parameters which converges to $(a, b, d)^{\top}$ for $l \to \infty$. Then we have the following.*

(1) *The sequence $\big(\mathbf{x}^{(l)}(t)\big)_{l=1}^{\infty}$ of solutions of the equation (4.12) corresponding to the initial conditions $\mathbf{x}^{(l)}(0) = (I, 0, a_l, b_l, d_l)^{\top}$ converges uniformly on $[0, T]$ to the solution $\mathbf{x}(t)$ of (4.12) with the initial condition $\mathbf{x}(0) = (I, 0, a, b, d)^{\top}$.*

(2) *If $\mathbf{y}^{(k)}(t)$ is the solution of the equation*

$$\dot{\mathbf{y}} = \mathbf{g}\big(\mathbf{x}^{(k-1)}\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}\big)\big(\mathbf{y} - \mathbf{x}^{(k-1)}\big)$$

on $[0, T]$ with the initial condition $\mathbf{y}^{(k)}(0) = (I, 0, a_k, b_k, d_k)^{\top}$ then for every $\eta > 0$ there is a $k_0 \in \mathbb{N}$ such that for every $k \in \mathbb{N}$, $k \geqslant k_0$ we have

$$\big\|\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big\| < \eta$$

for every $t \in [0, T]$, i.e.

$$\lim_{k \to \infty} \big\|\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big\| = 0$$

uniformly on $[0, T]$.

Remark 4.5. In fact $\mathbf{y}^{(k)}(t)$ is a solution of (4.15) with $\tilde{\mathbf{x}}(t) = \mathbf{x}^{(k-1)}(t)$ satisfying $\mathbf{y}^{(k)}(0) = (I, 0, a_k, b_k, d_k)^\top$ and it can be expressed in the form

$$\mathbf{y}^{(k)}(t) = \mathbf{p}^{(k)} + a_k \mathbf{h}_k^{(1)} + b_k \mathbf{h}_k^{(2)} + d_k \mathbf{h}_k^{(3)}$$

where $\mathbf{p}^{(k)}(t)$ is the particular solution of (4.15) with $\tilde{\mathbf{x}}(t) = \mathbf{x}^{(k-1)}(t)$ and $\mathbf{h}_k^{(1)}(t)$, $\mathbf{h}_k^{(2)}(t)$, $\mathbf{h}_k^{(3)}(t)$ are the solutions of the corresponding homogenous system, see (4.5), (4.6), (4.7) or (4.16), (4.17), (4.19) in our special case.

Proof of Lemma 4.4. The first part is an easy consequence of the continuous dependence of solutions of (4.12) on the initial values.

Concerning the second part we have for $t \in [0, T]$ by definition

$$\frac{\mathrm{d}}{\mathrm{d}t}\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big) = \mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big).$$

Integrating this relation from 0 to $s \in [0, T]$ and using the fact that $\mathbf{y}^{(k)}(0) - \mathbf{x}^{(k)}(0) = 0$ we get

$$\begin{aligned}
&\mathbf{y}^{(k)}(s) - \mathbf{x}^{(k)}(s) \\
&= \int_0^s \mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big)\,\mathrm{d}t \\
&= \int_0^s \mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big)\,\mathrm{d}t \\
&\qquad + \int_0^s \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big)\,\mathrm{d}t.
\end{aligned}$$

Hence

$$\begin{aligned}
&\big\|\mathbf{y}^{(k)}(s) - \mathbf{x}^{(k)}(s)\big\| \\
&\leqslant \int_0^s \big\|\mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big)\big\|\,\mathrm{d}t \\
&\qquad + \int_0^s \big\|\mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big)\big\|\,\mathrm{d}t \\
&\leqslant \int_0^T \big\|\mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big)\big\|\,\mathrm{d}t \\
&\qquad + \int_0^s \big\|\mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big\|\,\big\|\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big)\big\|\,\mathrm{d}t.
\end{aligned}$$

By Lemma 4.3 for every $\varepsilon > 0$ there is a $k_0 \in \mathbb{N}$ such that for every $k \geqslant k_0$ we have

$$\int_0^T \big\|\mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) - \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k-1)}(t) - \mathbf{x}^{(k)}(t)\big)\big\|\,\mathrm{d}t < 3\varepsilon^2 T.$$

Using the previous estimate we obtain

$$\left\|\mathbf{y}^{(k)}(s)-\mathbf{x}^{(k)}(s)\right\| \leqslant 3\varepsilon^2 T+\int_0^s \left\|\mathbf{J}(\mathbf{x}^{(k-1)}(t))\right\| \left\|\left(\mathbf{y}^{(k)}(t)-\mathbf{x}^{(k)}(t)\right)\right\| \mathrm{d}t$$

for every $s \in [0,T]$, and by the Gronwall lemma we get the estimate

$$\left\|\mathbf{y}^{(k)}(s)-\mathbf{x}^{(k)}(s)\right\| \leqslant 3\varepsilon^2 T \mathrm{e}^{\int_0^s \|\mathbf{J}(\mathbf{x}^{(k-1)}(t))\| \,\mathrm{d}t} \leqslant 3\varepsilon^2 T \mathrm{e}^{Q},$$

for any $s \in [0,T]$, where

$$Q=\int_0^T \left\|\mathbf{J}\left(\mathbf{x}^{(k-1)}(t)\right)\right\| \mathrm{d}t<\infty,$$

because the sequence $\left(\mathbf{x}^{(k)}(t)\right)_{k=1}^{\infty}$ is bounded on the interval $[0,T]$ (this is the consequence of the first assertion). If we take $\varepsilon=\sqrt{\eta/(3T\mathrm{e}^{Q})}>0$ then we obtain immediately the assertion of the lemma. □

Corollary 4.6. *If the assumptions of Lemma* 4.4 *are satisfied then*

$$\lim_{k\to\infty}\left\|\mathbf{y}^{(k)}(t)-\mathbf{x}(t)\right\|=0$$

uniformly on $[0,T]$.

Theorem 4.7. *Assume that* $T>0$ *is given. Let* $\left(\mathbf{x}^{(l)}(t)\right)_{l=1}^{\infty}$ *be a sequence of solutions of the initial value problem* (4.12), (4.13), *corresponding to* $\alpha=(a_l,b_l,d_l)$ *which uniformly converges on the interval* $[0,T]$, *and let* $\mathbf{y}^{(k)}(t)$ *be the solution of the equation*

$$\dot{\mathbf{y}}=\mathbf{g}\left(\mathbf{x}^{(k-1)}\right)+\mathbf{J}\left(\mathbf{x}^{(k-1)}\right)\left(\mathbf{y}-\mathbf{x}^{(k-1)}\right)$$

on the interval $[0,T]$ *with the initial condition* $\mathbf{y}^{(k)}(0)=(I,0,a_k,b_k,d_k)^{\top}$.

Then

$$\lim_{k\to\infty}\left\|S\left(\mathbf{y}^{(k)}\right)-S\left(\mathbf{x}^{(k)}\right)\right\|=0$$

where $S(\mathbf{x})$ *is described in* (4.23).

Proof. Our assertion follows from Lemma 4.4 and from the fact that the terms $(x-r_i)^2$, $i=1,\ldots,L$, and $((I-x-y)-e_j)^2$, $j=1,\ldots,M$, occuring in (4.23) are continuous as functions of a vector $\mathbf{x}=(x,y,a,b,d)^{\top}$. □

Remark 4.8. All the previous statements depend on the fact that we have at our disposal a uniformly convergent sequence $\mathbf{x}^{(k)}(t)$ of solutions of the initial value problem (4.12), (4.13).

5. Numerical results

For numerical computations we have seven data sets $M_1, \ldots M_7$ of measured values of BSP in the blood (at times t_i) and in the bile (at times e_j) which are indicated in the following graphs by dots. Characterization of the measurement was given in the part describing the clinical data.

The first four cases $M_1, \ldots, M_4$ give measurements for the same person. The BSP-test was done on the 6th, 25th, 26th and 27th day after cholecystectomy in this case. The initial amount of BSP was different, e.g. 125, 250 and 500 mg, respectively. Since the modelling system (1.1) is linear (its solutions form a linear space) the measured data can be modified to data which correspond to the uniform initial dose of BSP—250 mg for all cases.

For obtaining numerical results the Mathematica software package was used. Three methods have been examined.

(1) FM—this method uses the analytical solution (2.1), (2.2) and the Mathematica command `FindMinimum` is applied to the function (3.1).

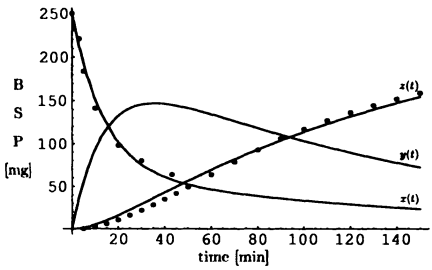
(2) QM—this is the Quasilinearization method described in the previous section.

(3) QFM—this method is a modification of QM. We do not solve the algebraic equations (4.9), the command `FindMinimum` for the function (4.21) is applied instead.

The numerical results, presenting the unknown parameters a, b, d, for the given cases are shown in the following tables. The corresponding graphs represent the solutions to (4.12), (4.13) for the values of the parameters a, b, d obtained by the Quasilinearization method.

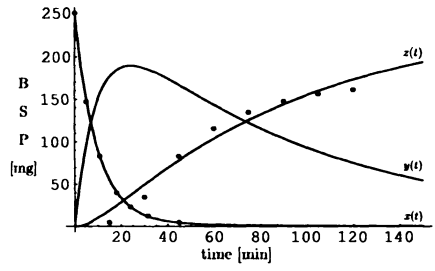
	a	b	d	steps
FM	0.054736	0.0152704	0.0093906	4
QFM	0.054736	0.0152704	0.0093906	11
Q	0.054736	0.0152704	0.0093906	13

Table 1. Numerical results for case M_1.



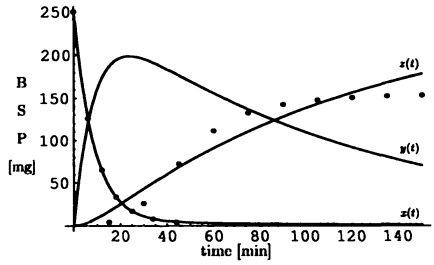
	a	b	d	steps
FM	0.1028669	0.0012472	0.0109183	3
QFM	0.1028669	0.0012472	0.0109183	8
Q	0.1028669	0.0012471	0.0109183	19

Table 2. Numerical results for case M_2.



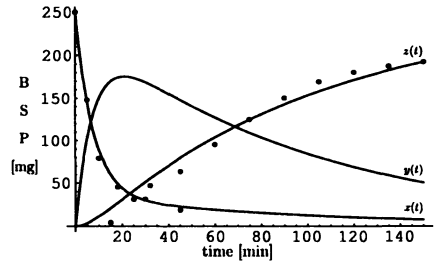
	a	b	d	steps
FM	0.1155239	0.0020142	0.009009	4
QFM	0.1155235	0.0020141	0.009009	11
Q	0.1155235	0.0020141	0.009009	17

Table 3. Numerical results for case M_3.



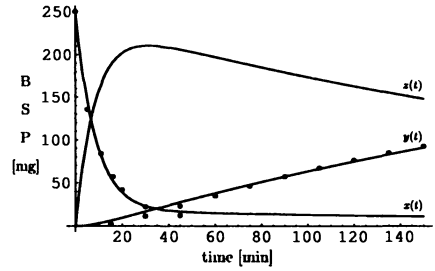
	a	b	d	steps
FM	0.1146878	0.0154462	0.0118261	3
QFM	0.1146877	0.0154462	0.0118261	8
Q	0.1146877	0.0154462	0.0118261	11

Table 4. Numerical results for case M_4.



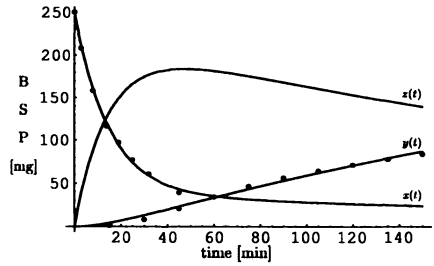
	a	b	d	steps
FM	0.1098251	0.0079839	0.0034339	6
QFM	0.1098253	0.0079840	0.0034339	10
Q	0.1098253	0.0079840	0.0034339	10

Table 5. Numerical results for case M_5.



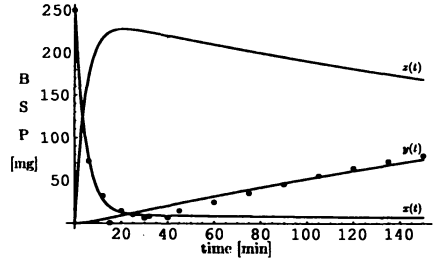
	a	b	d	steps
FM	0.0579301	0.0093114	0.0037127	5
QFM	0.0579301	0.0093114	0.0037127	9
Q	0.0579301	0.0093114	0.0037127	10

Table 6. Numerical results for case M_6.



	a	b	d	steps
FM	0.2070551	0.0085127	0.0025377	8
QFM	0.2070551	0.0085127	0.0025377	8
Q	0.2070550	0.0085127	0.0025377	9

Table 7. Numerical results for case M_7.



In the last column in Tables 1–7 we mention how many iterations were needed in the computation. We used the criterion (4.11) for $\varepsilon = 10^{-7}$. In the case when the analytical solution (FM method) is used, the least number of computing steps was needed. We must note that the number of steps for all methods depends on the initial choice α_1. For all cases in our tables the same starting value $\alpha_1 = (0.107, 0.004, 0.01)$ of the parameters was used.

According to the medical point of view [3], the satisfactory clinical status of the patient corresponds to the interval $[0.102, 0.116]$ of the parameter a. The meaning of values of parameters b, d for the characterization of liver function is not known at present and it should be interpreted on a larger sample of data.

References

[1] *R. Bellman, R. Roth*: Quasilinearization and the Identification Problem. World Scientific, Singapore, 1983.

[2] *P. Hartman*: Ordinary Differential Equations. S. M. Hartman, Baltimore, 1973.

[3] *E. Hrnčíř*: Personal notes. Unpublished.

[4] *R. Kalaba, K. Spingarn*: Control, Identification, and Input Optimization. Mathematical Concepts and Methods in Science and Engineering, Vol. 25. Plenum Press, New York-London, 1982.

[5] *J. M. Watt, A. Young*: An attempt to simulate the liver on a computer. Comput. J. *5* (1962), 221–227.

Author's address: *L. Čelechovská*, Mathematical Institute, Silesian University, Na Rybníčku 1, 746 01 Opava, Czech Republic, e-mail: Lenka.Celechovska@math.slu.cz.

49 (2004) APPLICATIONS OF MATHEMATICS No. 3, 227–246

A SIMPLE MATHEMATICAL MODEL OF THE HUMAN LIVER

Lenka Čelechovská, Opava

(Received March 4, 2002)

Abstract. The parameter estimation problem for a continuous dynamical system is a difficult one. In this paper we study a simple mathematical model of the liver. For the parameter identification we use the observed clinical data obtained by the BSP test. Bellman's quasilinearization method and its modifications are applied.

Keywords: identification of parameters, quasilinearization method

MSC 2000: 34B60, 92C50

1. The physiological problem and a simple mathematical model

This note is devoted to the problem of mathematical modelling of the liver functions. The mathematics concerning the models should be done in such a way that data given by clinical experiments on humans would give relevant information on the status of an individual. Let us shortly describe the basic procedure for obtaining data.

Bromsulphthalein (BSP) is a colouring matter, which is injected into the blood. The liver is the only organ which takes BSP and secretes BSP directly into the bile, i.e. we can assume that the BSP is not taken up by any other organ in the body. The level of BSP in the blood is measured at different times t. This procedure is relatively simple from the practical point of view; it gives a finite sequence of values showing the more or less rapid decrease of BSP in the blood and is used for investigation of the function of the liver.

Denote by x, y, z the amount of BSP in the blood, in the liver and in the bile at time t, respectively.

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 in the form of the

system of linear ordinary differential equations

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= -ax + by, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= ax - (b+d)y, \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= dy. \end{aligned} \tag{1.1}$$

The constants a, b, d are the rates of transfer and they are unknown. In this way the mathematical model describing the liver function was presented in [5].

Suppose that there is a "single injection", in which some quantity $I > 0$ of BSP is injected into the blood at once. This leads to initial conditions

$$x(0) = I, \quad y(0) = 0, \quad z(0) = 0, \quad I > 0 \tag{1.2}$$

for the system (1.1). The constants a, b, d characterize the system and in some sense they should characterize the clinical status of the human. How reliable information of this kind is, is not very clear at this moment.

Let us note that the quantity $z(t)$ can be looked upon as the efflux of BSP from the system which is investigated and that from the viewpoint of the dynamics of the process it plays a role which is not very essential. The value of $z(t)$ can be reconstructed from the knowledge of $x(t)$ and $y(t)$. Indeed, looking at the system we can see immediately, by adding the equations in (1.1), that

$$\frac{\mathrm{d}(x+y+z)}{\mathrm{d}t} = 0$$

and

$$x(0) + y(0) + z(0) = I.$$

This means that

$$x(t) + y(t) + z(t) = I \tag{1.3}$$

for all $t \geqslant 0$ and

$$z(t) = I - x(t) - y(t)$$

for $t \geqslant 0$.

Therefore it is enough to consider the lower dimensional system of linear ordinary differential equations

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= -ax + by, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= ax - (b+d)y \end{aligned} \tag{1.4}$$

subject to the initial conditions

$$x(0) = I, \quad y(0) = 0, \quad I > 0. \tag{1.5}$$

Note that the constants a, b, d occuring in the system (1.1) have to be positive since they represent the rates of decay of BSP from the blood and the liver. Therefore we assume in the sequel that

$$a > 0, \quad b > 0, \quad d > 0.$$

The clinical test described above gives information on the numerical values of $x(t)$ for some finite number of instants t.

Assume that the function x is known for all t in an interval $[0, T]$, $T > 0$ and investigate the problem how much information about the system, i.e. about the constants a, b, d, is contained in this knowledge.

Let us suppose another system is given and that it has the same structure as (1.4) but the coefficients are different:

$$\begin{aligned} \frac{\mathrm{d}X}{\mathrm{d}t} &= -AX + BY, \\ \frac{\mathrm{d}Y}{\mathrm{d}t} &= AX - (B + D)Y. \end{aligned} \tag{1.6}$$

Assume that for the first component $X(t)$ of the solution we have

$$x(t) = X(t) \tag{1.7}$$

if $t \in [0, T]$. Then

$$\dot{x}(t) = \dot{X}(t)$$

for $t \in [0, T]$, consequently

$$-ax(t) + by(t) = -AX(t) + BY(t)$$

and

$$AX(t) - ax(t) = (A - a)x(t) = BY(t) - by(t).$$

Since $Y(0) = y(0) = 0$ and $x(0) = I > 0$ we obtain

$$A = a \tag{1.8}$$

and

$$y(t) = \frac{B}{b} Y(t).$$

Using the equality

$$\dot{y}(t) + (b+d)y(t) = ax(t) = AX(t) = \dot{Y}(t) + (B+D)Y(t)$$

and (1.8) we get

$$\dot{y}(t) - \dot{Y}(t) = \dot{Y}(t)\Big(\frac{B}{b} - 1\Big) = Y(t)\Big(D - \frac{dB}{b}\Big).$$

Since $Y(0) = 0$ and $\dot{Y}(0) = AI > 0$ we obtain

$$b = B$$

and consequently $d = D$.

This shows that in our case the system is uniquely determined. This means that the coefficients in (1.4) are determined uniquely. Let us mention that if we know the efflux $z(t)$ on the interval $[0, T]$, then by the relation (1.3) the values of $y(t)$ are also known on $[0, T]$ and the knowledge of $z(t)$ leads also to the unicity of the mathematical model.

Of course this mathematical fact leads to technical problems. The amounts of BSP in the bile can be measured only in the case when the patient is after a cholecystectomy and a drain takes out all the bile from the body. The efflux is known in this case and there is a theoretical possibility to identify the system, i.e. to determine the coefficients a, b and d.

2. Some properties of the system

The process of development of the amounts of BSP in the blood and liver is described by the relatively simple linear model of ODE's presented in the previous section.

It is easy to see that the equilibrium points of the system (1.4) are given by the solutions of the algebraic system

$$\begin{aligned} -ax + by &= 0, \\ ax - (b+d)y &= 0. \end{aligned}$$

It can be seen easily that there is only one equilibrium point $P = (0, 0)$ under the assumption $a > 0$, $b > 0$, $d > 0$.

Let us investigate the stability of the system (1.4) at the point P. The matrix of the system (1.4) is

$$A = \begin{pmatrix} -a & b \\ a & -b-d \end{pmatrix}$$

and the characteristic values of this matrix, given by the algebraic equation

$$\det(A - \lambda E) = \lambda^2 + \lambda(a + b + d) + ad = 0,$$

are

$$\lambda_{1,2} = \frac{-(a + b + d) \pm \sqrt{(a + b + d)^2 - 4ad}}{2}.$$

If a, b and d are positive, then

$$|a + b + d|^2 > (a + b + d)^2 - 4ad \geqslant 0,$$

and so the characteristic values $\lambda_{1,2}$ are negative, which means that the solution $x(t) = 0$, $y(t) = 0$ corresponding to the equilibrium P of (1.4) is globally asymptoticaly stable.

Besides these basic qualitative properties of a solution to the system (1.4) we can express explicitly the solution to the initial value problem (1.4), (1.5) in the form

$$x(t) = \frac{(a - b - d)I}{2\sqrt{(a + b + d)^2 - 4ad}}\left(\mathrm{e}^{\lambda_2 t} - \mathrm{e}^{\lambda_1 t}\right) + \frac{I}{2}\left(\mathrm{e}^{\lambda_1 t} + \mathrm{e}^{\lambda_2 t}\right), \tag{2.1}$$

$$y(t) = -\frac{a\left(-\mathrm{e}^{\lambda_1 t} + \mathrm{e}^{\lambda_2 t}\right)I}{\sqrt{(a + b + d)^2 - 4ad}}. \tag{2.2}$$

3. Clinical data

The structure of data describing the decay of BSP in the blood is given by a finite set of times $t_1, t_2, \ldots, t_L$ at which the amounts $r_1, r_2, \ldots, r_L$ of BSP are measured. The first time is $t_1 = 0$ and the corresponding value of r_1 is the value corresponding to the injection I administered to the patient.

At the finite set of times $s_1, s_2, \ldots, s_M$ the amounts of the efflux $e_1, e_2, \ldots, e_M$ of BSP into the bile are measured.

Note that this last measurement was possible only in the case that a drain was inserted into the channel connecting the liver with the gall-bladder. As it was mentioned above a cholecystectomy makes this possible in some cases.

Let us present a typical set of clinical data. The measured values of the amount of BSP in the blood are given in the following table.[1]

t_i	0	3	5	10	20	30	43
r_i	250	221	184	141	98	80	64

[1] All the data presented in this work were obtained by Prof. Evžen Hrnčíř in 1985. New technologies today can maybe give similar data sets without the invasive technology of a cholecystectomy.

The measured efflux into the bile is presented in the following table.

s_j	5	10	15	20	25	30	35	40	45	50
e_j	0.2	2.5	6	10.5	15.8	21.7	28	34.8	41.8	49

s_j	60	70	80	90	100	110	120	130	140	150
e_j	63.8	78.5	92.7	105.7	117	127.1	136.3	144.5	152.1	159.2

The aim is to find the coefficients a, b and d of the system of ordinary differential equations (1.4) subject to the initial conditions (1.5) which in some sense correspond to the measured data of this type. The concept of correspondence will be described bellow.

Since by (2.1), (2.2) the exact solution to (1.4), (1.5) is known, the deviation of the exact solution from the observed data can be expressed in the form

$$S = \sum_{i=1}^{L} (x(t_i) - r_i)^2 + \sum_{j=1}^{M} (z(s_j) - e_j)^2,$$

where $z(t)$ is the efflux at the time t given by (1.3).

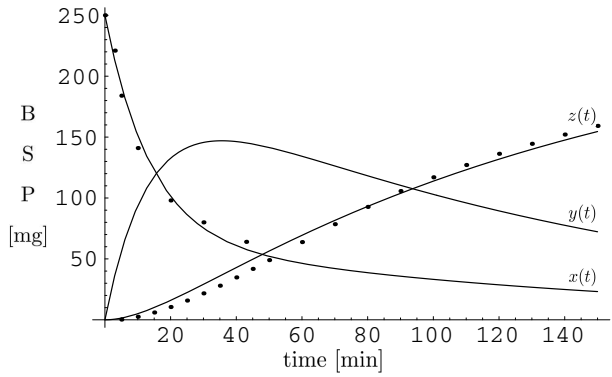
So we have in fact

$$S = \sum_{i=1}^{L} (x(t_i) - r_i)^2 + \sum_{j=1}^{M} ((I - x(s_j) - y(s_j)) - e_j)^2. \tag{3.1}$$

The nonnegative value of the deviation S depends of course on the parameters a, b and d of the system (1.4) and this value has to be minimized with respect to a, b and d.

It is clear that it is a difficult task to find the minimum of S and that numerical methods have to be used there. The Mathematica program package can be used for concrete computations. Using the `FindMinimum` command of Mathematica gives for the presented set of clinical data the approximate result that the function S attains its minimum $S = 862.546$ at $a = 0.0547241$, $b = 0.0152577$, $d = 0.00939036$.

Representing this result graphically we obtain the picture which shows that the values of x and z for the exact solution to the system (1.4), (1.5) are close to the measured clinical values indicated by dots in the picture.



4. Quasilinearization method

The main method in system identification is the quasilinearization technique which will be described in this part. This method was first used by R. Bellman [1]. The method consists in the construction of a sequence of functions $\mathbf{x}^n(t)$ which converges to the solution of the differential equation in such a way that the deviation S goes to its (local) minimum. The general formulation of this method for system identification is described in detail in [4]. We must emphasize that good convergence results can be achieved when we have a good initial approximation $\mathbf{x}^1(t)$.

We shall work in the finite-dimensional space $\mathbb{R}^m$. The norm $\|x\|$ of a vector $x = (x_1, \ldots, x_m)^\top$ is[2]

$$\|x\| := \max_{i=1,\ldots,m} |x_i|.$$

If $A = (a_{ij})$, $i, j = 1, \ldots, m$ is an $m \times m$-matrix, then $\|A\|$ denotes the (operator) norm corresponding to the given norm of m-vectors. For the norm of an m-vector presented above the norm of a matrix is given by

$$\|A\| := \max_{i=1,\ldots,m} \sum_{j=1}^{m} |a_{ij}|.$$

4.1. The general formulation

Consider a nonlinear autonomous system of ordinary differential equations

$$\dot{x}(t) = f(x(t), \boldsymbol{\alpha}), \tag{4.1}$$

where $x(t) = (x_1(t), \ldots, x_n(t))^\top$ is an n-dimensional vector, $\alpha = (\alpha_1, \ldots, \alpha_N)^\top$ is an N-dimensional vector of parameters and $f\colon\ \mathbb{R}^n \times \mathbb{R}^N \to \mathbb{R}^n$ is a continuous function

[2] By the symbol $^\top$ we denote the transposition of a matrix, e.g. $(x_1, \ldots, x_m)^\top$ is the column vector with components $x_1, \ldots, x_m$.

of (x, α) having continuous bounded partial derivatives with respect to x and α for all (x, α) in the region of interest.

For the system (4.1) consider the initial value problem

$$x_j(0) = c_j, \quad j = 1, \dots, n, \tag{4.2}$$

with known values of c_j, $j = 1, \dots, n$. The N parameters α are arbitrary.

Consider the constant vector α to be a function of time that satisfies the differential equation

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

Define $\mathbf{x}(t)$ as an $(n + N)$-dimensional vector and a vector $\mathbf{c}$ (corresponding to the initial conditions) as follows

$$\mathbf{x}(t) = (x_1(t), \dots, x_n(t), \alpha_1(t), \dots, \alpha_N(t))^\top,$$
$$\mathbf{c} = (c_1, \dots, c_n, \nu_1, \dots, \nu_N)^\top.$$

Assume that $\mathbf{g}(\mathbf{x}(t)) = (f(x(t), \alpha), \underbrace{0, \dots, 0}_{N})^\top$.

If $x(t)$ is a solution of the system (4.1) with (4.2) and with $\alpha_j = \nu_j$, $j = 1, \dots, N$, then the vector $\mathbf{x}(t) = (x(t), \alpha(t))^\top$ is a solution of the initial value problem

$$\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x}), \quad \mathbf{x}(0) = \mathbf{c}, \tag{4.3}$$

and, conversely, if $\mathbf{x}(t)$ is a solution of (4.3) then the first n components of this solution represent a solution of (4.1) with (4.2) and with $\alpha_j = \nu_j$, $j = 1, \dots, N$.

Given a fixed solution $\widetilde{\mathbf{x}}(t)$ of the differential equation (4.3), the system (4.3) can be linearized around this solution.

The linearized system has the form

$$\dot{\mathbf{y}} = \mathbf{g}(\widetilde{\mathbf{x}}) + \mathbf{J}(\widetilde{\mathbf{x}})(\mathbf{y} - \widetilde{\mathbf{x}}), \tag{4.4}$$

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

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

in the ith row and jth column, $i, j = 1, \dots, n + N$, and we use it for $\mathbf{x} = \widetilde{\mathbf{x}}(t)$ in the equation (4.4).

The equation (4.4) represents a linear system of $n + N$ differential equations for $\mathbf{y}$ and its solution $\mathbf{y}(t)$ for which $\mathbf{y}_j(0) = c_j$, $j = 1, \dots, n$, can be represented in the form

$$\mathbf{y}(t) = \mathbf{p}(t) + \sum_{j=1}^{N} \beta_j \mathbf{h}^{(j)}(t) \tag{4.5}$$

where $\mathbf{p}(t)$ is the (particular) solution of

$$\dot{\mathbf{p}} = \mathbf{g}(\widetilde{\mathbf{x}}) + \mathbf{J}(\widetilde{\mathbf{x}})(\mathbf{p} - \widetilde{\mathbf{x}}) \tag{4.6}$$

with the initial condition

$$\mathbf{p}_j(0) = c_j, \;\; j = 1, \dots, n, \quad \mathbf{p}_{l+n}(0) = 0, \;\; l = 1, \dots, N,$$

and $\mathbf{h}^{(j)}(t)$, $j = 1, \dots, N$, are solutions of the homogeneous system

$$\dot{\mathbf{h}}^{(j)} = \mathbf{J}(\widetilde{\mathbf{x}})\mathbf{h}^{(j)} \tag{4.7}$$

with $\mathbf{h}_i^{(j)}(0) = 0$ for $i \neq j + n$, $i = 1, \dots, n + N$, and $\mathbf{h}_{j+n}^{(j)}(0) = 1$.

Further we prove the following lemma.

Lemma 4.1. *Assume that $\widetilde{\mathbf{x}}(t)$ is a solution of the initial value problem* (4.3) *and that $\mathbf{y}(t)$ is a solution of the equation* (4.4) *in the form* (4.5) *with the initial conditions*

$$\mathbf{y}_j(0) = \begin{cases} c_j, & \text{for } j = 1, \dots, n \\ \beta_{j-n}, & \text{for } j = n+1, \dots, n+N. \end{cases} \tag{4.8}$$

If, moreover, $\nu_i = \beta_i$, $i = 1, \dots, N$, then

$$\mathbf{y}(t) = \widetilde{\mathbf{x}}(t)$$

for $t \geqslant 0$, i.e. the solution of the linearized equation (4.4) *coincides with the solution $\widetilde{\mathbf{x}}(t)$ of* (4.3) *in this case.*

P r o o f. For the difference $\mathbf{y}(t) - \widetilde{\mathbf{x}}(t)$ we have the following differential equation

$$\frac{\mathrm{d}}{\mathrm{d}t}(\mathbf{y} - \widetilde{\mathbf{x}}) = \mathbf{g}(\widetilde{\mathbf{x}}) + \mathbf{J}(\widetilde{\mathbf{x}})(\mathbf{y} - \widetilde{\mathbf{x}}) - \mathbf{g}(\widetilde{\mathbf{x}}) = \mathbf{J}(\widetilde{\mathbf{x}})(\mathbf{y} - \widetilde{\mathbf{x}}).$$

Integrating this equation from 0 to t we have

$$\mathbf{y}(t) - \widetilde{\mathbf{x}}(t) = \mathbf{y}(0) - \widetilde{\mathbf{x}}(0) + \int_0^t \mathbf{J}(\widetilde{\mathbf{x}}(s))(\mathbf{y}(s) - \widetilde{\mathbf{x}}(s))\,\mathrm{d}s$$

and

$$\begin{aligned} \|\mathbf{y}(t) - \widetilde{\mathbf{x}}(t)\| &\leqslant \|\mathbf{y}(0) - \widetilde{\mathbf{x}}(0)\| + \int_0^t \|\mathbf{J}(\widetilde{\mathbf{x}}(s))\|\|\mathbf{y}(s) - \widetilde{\mathbf{x}}(s)\|\,\mathrm{d}s \\ &= \|\mathbf{y}(0) - \mathbf{c}\| + \int_0^t \|\mathbf{J}(\widetilde{\mathbf{x}}(s))\|\|\mathbf{y}(s) - \widetilde{\mathbf{x}}(s)\|\,\mathrm{d}s. \end{aligned}$$

By the Gronwall lemma we obtain

$$\|\mathbf{y}(t) - \widetilde{\mathbf{x}}(t)\| \leqslant \|\mathbf{y}(0) - \mathbf{c}\| \cdot \exp\left(\int_0^t \|\mathbf{J}(\widetilde{\mathbf{x}}(s))\|\,\mathrm{d}s\right).$$

Since $\mathbf{y}(0) = \mathbf{c}$, we have $\mathbf{y}(t) = \widetilde{\mathbf{x}}(t)$ for $t \geqslant 0$. □

From (4.5) we can see immediately that the dependence of $\mathbf{y}(t)$ 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 a certain expression S which measures the deviation of the solution $\mathbf{y}(t)$ to (4.4) from some observed state.

The function S be of the following form

$$\begin{aligned} S(\mathbf{y}) &= S(\beta_1, \ldots, \beta_N) \\ &= \sum_{l=1}^{n} \sum_{i=1}^{L_l} \big(\mathbf{y}_l(t_i^l) - r_i^l\big)^2 + \sum_{j=1}^{M} \left(\left(\gamma + \sum_{l=1}^{n} \gamma_l \mathbf{y}_l(s_j) \right) - e_j \right)^2 \end{aligned}$$

where γ, γ_l, $l = 1, \ldots, n$, are some constants, t_i^l and s_j are some instants of time at which the experimental data r_i^l and e_j are known for the components of the solutions or some of their linear combinations.

In view of (4.5), we observe that $S(\mathbf{y})$ is a quadratic form in the variables $\beta_1, \ldots, \beta_N$. If this quadratic form is well behaved, the necessary conditions for finding its local minimum are given by

$$\frac{\partial S}{\partial \beta_j} = 0, \quad j = 1, \ldots, N, \tag{4.9}$$

which is a linear system of N algebraic equations for N unknown variables $\beta_1, \ldots, \beta_N$. Denote $\beta_1^*, \ldots, \beta_N^*$ the solution of this system.[3]

In any case putting $\mathbf{c}^* = (c_1, \ldots, c_n, \beta_1^*, \ldots, \beta_N^*)^\top$ we have new initial conditions and the procedure can be repeated by finding a solution $\mathbf{x}^*(t)$ of the differential equation $\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x})$ with the new initial conditions $\mathbf{x}(0) = \mathbf{c}^*$, linearizing the equation around $\mathbf{x}^*(t)$ and computing new initial values as above.

In this way in fact an iterative procedure is given which consists in finding a sequence of parameters $\beta_1^{(k)}, \ldots, \beta_N^{(k)}$, $k = 1, 2, \ldots$, for which the sequence $S\big(\beta_1^{(k)}, \ldots, \beta_N^{(k)}\big)$ decreases to some local minimum of S.

From the practical point of view the iterative procedure has to be repeated until

$$\beta_j^{(k+1)} = \beta_j^{(k)}, \quad j = 1, \ldots, N \tag{4.10}$$

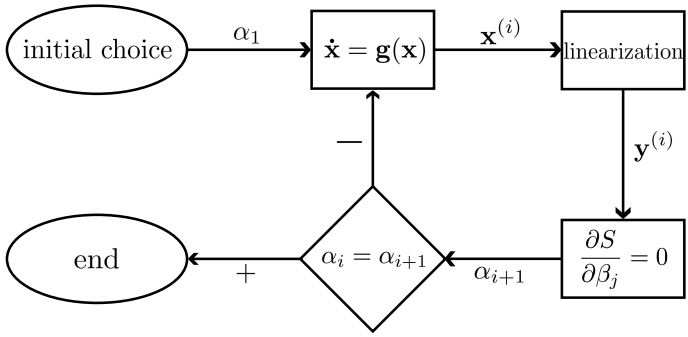
or

$$\big|\beta_j^{(k+1)} - \beta_j^{(k)}\big| < \varepsilon, \quad j = 1, \ldots, N \tag{4.11}$$

with some sufficiently small $\varepsilon > 0$.

[3] Using contemporary computational tools, e.g. the `FindMinimum` command in the Mathematica package, another way of finding the values $\beta_1^*, \ldots, \beta_N^*$ which minimize $S(\mathbf{y}) = S(\beta_1, \ldots, \beta_N)$ can be found.

R e m a r k 4.2. For the sake of clarity, we summarize the quasilinearization method in a flow diagram.



4.2. Application of the quasilinearization method

We apply the general quasilinearization method described above to the system (1.4). The problem (1.4) subject to the initial conditions (1.5) in fact corresponds to (4.1) with $\alpha = (a, b, d)^\top$, $f((x, y), \alpha) = (-ax + by, ax - (b + d)y)^\top$, and the initial condition (4.2) with $c = (I, 0)$; we have $n = 2$, $N = 3$ in this case.

We set

$$\mathbf{x} = (x, y, a, b, d)^\top.$$

The initial value problem (4.3) takes the form

$$\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x}), \tag{4.12}$$

$$\mathbf{x}(0) = \mathbf{c} = (I, 0, \alpha)^\top \tag{4.13}$$

where

$$\mathbf{g}(\mathbf{x}) = (-ax + by, ax - (b + d)y, 0, 0, 0)^\top. \tag{4.14}$$

The Jacobian matrix $\mathbf{J}(\mathbf{x})$ corresponding to this $\mathbf{g}(\mathbf{x})$ is given by

$$\mathbf{J}(\mathbf{x}) = \begin{pmatrix} -a & b & -x & y & 0 \\ a & -b-d & x & -y & -y \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Let us note that the function $\mathbf{g}\colon \mathbb{R}^5 \longrightarrow \mathbb{R}^5$ given by (4.14) is continuously differentiable. Therefore the solutions of (4.12) are uniquely determined by the initial

conditions. The last three components of any solution to (4.12) are constant and equal to the triple $\alpha = (a, b, d)$.

Hence the differential equation (4.12) has nice properties; in particular, the solutions depend continuosly on the initial conditions. Taking into account Section 2 and the fact that the only equlibrium $P = (0, 0)$ of the system (1.4) is globally asymptotically stable, we can see easily that for all solutions $\mathbf{x}(t)$, $t \geqslant 0$ of (4.12) with $\mathbf{x}(0) = (I, 0, a, b, d)$ we have

$$\mathbf{x}(t) \in [0, I] \times [0, I] \times [0, A] \times [0, B] \times [0, D] \subset \mathbb{R}^5$$

provided $0 < a \leqslant A$, $0 < b \leqslant B$, $0 < d \leqslant D$, i.e. these solutions are bounded in the future.

Using this fact we also obtain the boundedness of $\|\mathbf{J}(\mathbf{x}(t))\|$ for all $t \geqslant 0$, where $\mathbf{x}(t)$ is a solution of (4.12), if $0 < a \leqslant A$, $0 < b \leqslant B$, $0 < d \leqslant D$.

Given a solution $\widetilde{\mathbf{x}}(t)$ of (4.12), (4.13) for some choice $\alpha = (\widetilde{a}, \widetilde{b}, \widetilde{d})^\top$, or in other words a solution $(\widetilde{x}, \widetilde{y})^\top$ of (1.4) with these values of the parameters, the linearized system (4.4) around the solution $\widetilde{\mathbf{x}}(t)$ assumes the form

$$\dot{\mathbf{y}} = \mathbf{g}(\widetilde{\mathbf{x}}) + \mathbf{J}(\widetilde{\mathbf{x}})(\mathbf{y} - \widetilde{\mathbf{x}}), \tag{4.15}$$

where $\mathbf{y}(t) = (y_1(t), \dots, y_5(t))^\top$. The initial conditions for the first two components are fixed as $y_1(0) = I$, $y_2(0) = 0$, while the initial conditions for $y_3(0)$, $y_4(0)$, $y_5(0)$ are free.

Writing this system componentwise we obtain after a simplification the system

$$\begin{aligned}
\dot{y_1} &= -\widetilde{a}y_1 + \widetilde{b}y_2 - \widetilde{x}(y_3 - \widetilde{a}) + \widetilde{y}(y_4 - \widetilde{b}),\\
\dot{y_2} &= \widetilde{a}y_1 - (\widetilde{b} + \widetilde{d})y_2 + \widetilde{x}(y_3 - \widetilde{a}) - \widetilde{y}(y_4 - \widetilde{b}) - \widetilde{y}(y_5 - \widetilde{d}),\\
\dot{y_3} &= 0, \quad \dot{y_4} = 0, \quad \dot{y_5} = 0.
\end{aligned}$$

The general solution of this problem can be expressed in the form (4.5), i.e.

$$\mathbf{y}(t) = \mathbf{p}(t) + \sum_{j=1}^{3} \beta_j \mathbf{h}^{(j)}(t) \tag{4.16}$$

where the components $p_1(t), \dots, p_5(t)$ of $\mathbf{p}(t)$ satisfy

$$\begin{aligned}
\dot{p_1} &= -\widetilde{a}p_1 + \widetilde{b}p_2 - \widetilde{x}(p_3 - \widetilde{a}) + \widetilde{y}(p_4 - \widetilde{b}),\\
\dot{p_2} &= \widetilde{a}p_1 - (\widetilde{b} + \widetilde{d})p_2 + \widetilde{x}(p_3 - \widetilde{a}) - \widetilde{y}(p_4 - \widetilde{b}) - \widetilde{y}(p_5 - \widetilde{d}),\\
\dot{p_3} &= 0, \quad \dot{p_4} = 0 \quad \dot{p_5} = 0
\end{aligned} \tag{4.17}$$

with

$$p(0) = (I, 0, 0, 0, 0), \tag{4.18}$$

and for $\mathbf{h}^{(j)}(t)$, $j = 1, 2, 3$ we have for their components $h_1^{(j)}(t), \dots, h_5^{(j)}(t)$ the equations

$$\begin{aligned} \dot{h_1^{(j)}} &= -\widetilde{a}h_1^{(j)} + \widetilde{b}h_2^{(j)} - \widetilde{x}h_3^{(j)} + \widetilde{y}h_4^{(j)}, \\ \dot{h_2^{(j)}} &= \widetilde{a}h_1^{(j)} - (\widetilde{b} + \widetilde{d})h_2^{(j)} + \widetilde{x}h_3^{(j)} - \widetilde{y}h_4^{(j)} - \widetilde{y}h_5^{(j)}, \\ \dot{h_3^{(j)}} &= 0, \quad \dot{h_4^{(j)}} = 0, \quad \dot{h_5^{(j)}} = 0 \end{aligned} \tag{4.19}$$

and the initial conditions

$$\begin{aligned} h^{(1)}(0) &= (0, 0, 1, 0, 0)^\top, \\ h^{(2)}(0) &= (0, 0, 0, 1, 0)^\top, \\ h^{(3)}(0) &= (0, 0, 0, 0, 1)^\top. \end{aligned} \tag{4.20}$$

Using the deviation given by (3.1) in the part concerning the clinical data we write

$$\begin{aligned} S(\mathbf{y}) = S(\beta_1, \beta_2, \beta_3) &= \sum_{i=1}^{L} (y_1(t_i) - r_i)^2 \\ &+ \sum_{j=1}^{M} \big((I - y_1(s_j) - y_2(s_j)) - e_j\big)^2. \end{aligned} \tag{4.21}$$

In view of (4.16), this expression is clearly a quadratic form in β_1, β_2, β_3.

Now we can describe the iterative procedure coming from the quasilinearization method.

Let an initial choice $\alpha_1 = (a_1, b_1, d_1)$ of the parameters be given and let $\mathbf{x}^{(1)}(t)$ be the solution of (4.12) defined for $t \geqslant 0$ with the initial condition

$$\mathbf{x}^{(1)}(0) = (I, 0, a_1, b_1, d_1)^\top.$$

Linearizing (4.12) around $\mathbf{x}^{(1)}$ we get the equation

$$\dot{\mathbf{y}} = \mathbf{g}\big(\mathbf{x}^{(1)}\big) + \mathbf{J}\big(\mathbf{x}^{(1)}\big)\big(\mathbf{y} - \mathbf{x}^{(1)}\big), \tag{4.22}$$

and its solution can be expressed in the form (4.16) where $\mathbf{p}(t)$ and $\mathbf{h}^{(j)}(t)$ are given by the systems (4.17) and (4.19) with initial conditions given by (4.18) and (4.20), respectively, with $\widetilde{a} = a_1$, $\widetilde{b} = b_1$, $\widetilde{d} = d_1$. Using this form of a solution of the linearized equation (4.22) we consider the function $S(y) = S(\beta_1, \beta_2, \beta_3)$ given by (4.21)

and we find its (local) minimum (using some computational or mathematical tool), i.e. a point (a_2, b_2, d_2) at which $S(a_2, b_2, d_2) \leqslant S(a_1, b_1, d_1)$.

Note that by the considerations in the part describing the general form of quasi-linearization (see Lemma 4.1) we have $\mathbf{y}(t) = \mathbf{x}^{(1)}(t)$ if $\beta_1 = a_1$, $\beta_2 = b_1$, $\beta_3 = d_1$ and $S(a_1, b_1, d_1) = S(\mathbf{x}^{(1)})$ is the deviation of $\mathbf{x}^{(1)}(t)$.

Now the iterations are produced as follows.

Given $\alpha_k = (a_k, b_k, d_k)^\top$ let $\mathbf{x}^{(k)}(t)$ be the unique solution of (4.12) given for $t \geqslant 0$ by the initial condition

$$\mathbf{x}^{(k)}(0) = (I, 0, a_k, b_k, d_k)^\top$$

and consider the linearization

$$\dot{\mathbf{y}} = \mathbf{g}\big(\mathbf{x}^{(k)}\big) + \mathbf{J}\big(\mathbf{x}^{(k)}\big)\big(\mathbf{y} - \mathbf{x}^{(k)}\big).$$

We express its solution in the form (4.16) where $\mathbf{p}(t)$ and $\mathbf{h}^{(j)}(t)$ are again given by the systems (4.17) and (4.19) with initial conditions given by (4.18) and (4.20), respectively, with $\widetilde{a} = a_k$, $\widetilde{b} = b_k$, $\widetilde{d} = d_k$, and we look for the (local) minimum of $S(\mathbf{y}) = S(\beta_1, \beta_2, \beta_3)$ to get $\alpha_{k+1} = (a_{k+1}, b_{k+1}, d_{k+1})$ for which $S(a_{k+1}, b_{k+1}, d_{k+1}) \leqslant S(a_k, b_k, d_k)$. We assume that $\mathbf{x}^{(k+1)}(t)$ is the solution of (4.12) for $t \geqslant 0$ with the initial condition $\mathbf{x}^{(k+1)}(0) = (I, 0, a_{k+1}, b_{k+1}, d_{k+1})^\top$.

This iterative procedure leads to a sequence $\mathbf{x}^{(k)}(t) = \big(x^{(k)}(t), y^{(k)}(t), \alpha_k\big)$, where $\alpha_k = (a_k, b_k, d_k)$ is the sequence of parameters.

For a given function $\mathbf{x}(t) = (x(t), y(t), a(t), b(t), d(t))$, $t \in [0, T]$ denote

$$S(\mathbf{x}) = \sum_{i=1}^{L} (x(t_i) - r_i)^2 + \sum_{j=1}^{M} \big((I - x(s_j) - y(s_j)) - e_j\big)^2 \tag{4.23}$$

its deviation from the measured values r_i and e_j.

Let us denote $\mathbf{u} := (x, y, a, b, d)^\top$ and $\mathbf{v} := (\xi, \zeta, \chi, \psi, \omega)^\top$. Then

$$\begin{aligned}\mathbf{R} &:= \mathbf{g}(\mathbf{u}) - \mathbf{g}(\mathbf{v}) - \mathbf{J}(\mathbf{u})(\mathbf{u} - \mathbf{v}) \\ &= \big((x - \xi)(a - \chi) + (y - \zeta)(\psi - b), \\ &\quad (x - \xi)(\chi - a) + (y - \zeta)(b - \psi) + (y - \zeta)(d - \omega), 0, 0, 0\big)^\top\end{aligned}$$

and using the above mentioned norm of a vector we have

$$\begin{aligned}\|\mathbf{R}\| = {} & \max\big(|(x - \xi)(a - \chi) + (y - \zeta)(\psi - b)|, \\ & |(x - \xi)(\chi - a) + (y - \zeta)(b - \psi) + (y - \zeta)(d - \omega)|\big) \\ \leqslant {} & 3\|\mathbf{u} - \mathbf{v}\|^2.\end{aligned} \tag{4.24}$$

Lemma 4.3. *Assume that $T > 0$ is given. Let $\big(\mathbf{x}^{(l)}(t)\big)_{l=1}^{\infty}$ be a sequence of solutions of the equation (4.12) with initial conditions $\mathbf{x}^{(l)}(0) = (I, 0, a_l, b_l, d_l)^\top$ which uniformly converges on the interval $[0, T]$.*

Then for every $\varepsilon > 0$ there is a $k_0 \in \mathbb{N}$ such that for every $k_1, k_2 \geqslant k_0$ we have

$$\big\|\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big\| < \varepsilon, \quad t \in [0, T],$$

and putting

$$\mathbf{W}(t) = \mathbf{g}\big(\mathbf{x}^{(k_1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k_2)}(t)\big) - \mathbf{J}\big(\mathbf{x}^{(k_1)}(t)\big)\big(\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big)$$

we also have

$$\int_0^T \|\mathbf{W}(t)\| \,\mathrm{d}t < 3\varepsilon^2 T. \tag{4.25}$$

P r o o f. The first statement is the Bolzano-Cauchy condition for uniform convergence. Using this and (4.24) with $\mathbf{R} = \mathbf{W}(t)$ we have for $k_1, k_2 \geqslant k_0$

$$\begin{aligned}\int_0^s \big\|\mathbf{g}\big(\mathbf{x}^{(k_1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k_2)}(t)\big) - \mathbf{J}\big(\mathbf{x}^{(k_1)}(t)\big)\big(\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big)\big\| \,\mathrm{d}t \\ \leqslant \int_0^s \big\|\mathbf{x}^{(k_1)}(t) - \mathbf{x}^{(k_2)}(t)\big\|^2 \,\mathrm{d}t < 3\varepsilon^2 s\end{aligned} \tag{4.26}$$

and (4.25) clearly holds. □

Lemma 4.4. *Assume that $T > 0$ is given. Let $(a_l, b_l, d_l)^\top$, $l \in \mathbb{N}$, be a sequence of parameters which converges to $(a, b, d)^\top$ for $l \to \infty$. Then we have the following.*

(1) *The sequence $\big(\mathbf{x}^{(l)}(t)\big)_{l=1}^{\infty}$ of solutions of the equation (4.12) corresponding to the initial conditions $\mathbf{x}^{(l)}(0) = (I, 0, a_l, b_l, d_l)^\top$ converges uniformly on $[0, T]$ to the solution $\mathbf{x}(t)$ of (4.12) with the initial condition $\mathbf{x}(0) = (I, 0, a, b, d)^\top$.*

(2) *If $\mathbf{y}^{(k)}(t)$ is the solution of the equation*

$$\dot{\mathbf{y}} = \mathbf{g}\big(\mathbf{x}^{(k-1)}\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}\big)\big(\mathbf{y} - \mathbf{x}^{(k-1)}\big)$$

on $[0, T]$ with the initial condition $\mathbf{y}^{(k)}(0) = (I, 0, a_k, b_k, d_k)^\top$ then for every $\eta > 0$ there is a $k_0 \in \mathbb{N}$ such that for every $k \in \mathbb{N}$, $k \geqslant k_0$ we have

$$\big\|\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big\| < \eta$$

for every $t \in [0, T]$, i.e.

$$\lim_{k\to\infty} \big\|\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big\| = 0$$

uniformly on $[0, T]$.

R e m a r k 4.5. In fact $\mathbf{y}^{(k)}(t)$ is a solution of (4.15) with $\widetilde{\mathbf{x}}(t) = \mathbf{x}^{(k-1)}(t)$ satisfying $\mathbf{y}^{(k)}(0) = (I, 0, a_k, b_k, d_k)^\top$ and it can be expressed in the form

$$\mathbf{y}^{(k)}(t) = \mathbf{p}^{(k)} + a_k \mathbf{h}_k^{(1)} + b_k \mathbf{h}_k^{(2)} + d_k \mathbf{h}_k^{(3)}$$

where $\mathbf{p}^{(k)}(t)$ is the particular solution of (4.15) with $\widetilde{\mathbf{x}}(t) = \mathbf{x}^{(k-1)}(t)$ and $\mathbf{h}_k^{(1)}(t)$, $\mathbf{h}_k^{(2)}(t)$, $\mathbf{h}_k^{(3)}(t)$ are the solutions of the corresponding homogenous system, see (4.5), (4.6), (4.7) or (4.16), (4.17), (4.19) in our special case.

P r o o f of Lemma 4.4. The first part is an easy consequence of the continuous dependence of solutions of (4.12) on the initial values.

Concerning the second part we have for $t \in [0, T]$ by definition

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big) &= \mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) \\ &\quad + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big).\end{aligned}$$

Integrating this relation from 0 to $s \in [0, T]$ and using the fact that $\mathbf{y}^{(k)}(0) - \mathbf{x}^{(k)}(0) = 0$ we get

$$\begin{aligned}&\mathbf{y}^{(k)}(s) - \mathbf{x}^{(k)}(s) \\ &= \int_0^s \mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big)\,\mathrm{d}t \\ &= \int_0^s \mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big)\,\mathrm{d}t \\ &\quad + \int_0^s \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big)\,\mathrm{d}t.\end{aligned}$$

Hence

$$\begin{aligned}&\big\|\mathbf{y}^{(k)}(s) - \mathbf{x}^{(k)}(s)\big\| \\ &\leqslant \int_0^s \big\|\mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big)\big\|\,\mathrm{d}t \\ &\quad + \int_0^s \big\|\mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big)\big\|\,\mathrm{d}t \\ &\leqslant \int_0^T \big\|\mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) + \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k)}(t) - \mathbf{x}^{(k-1)}(t)\big)\big\|\,\mathrm{d}t \\ &\quad + \int_0^s \big\|\mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big\|\,\big\|\big(\mathbf{y}^{(k)}(t) - \mathbf{x}^{(k)}(t)\big)\big\|\,\mathrm{d}t.\end{aligned}$$

By Lemma 4.3 for every $\varepsilon > 0$ there is a $k_0 \in \mathbb{N}$ such that for every $k \geqslant k_0$ we have

$$\int_0^T \big\|\mathbf{g}\big(\mathbf{x}^{(k-1)}(t)\big) - \mathbf{g}\big(\mathbf{x}^{(k)}(t)\big) - \mathbf{J}\big(\mathbf{x}^{(k-1)}(t)\big)\big(\mathbf{x}^{(k-1)}(t) - \mathbf{x}^{(k)}(t)\big)\big\|\,\mathrm{d}t < 3\varepsilon^2 T.$$

Using the previous estimate we obtain

$$\left\|\mathbf{y}^{(k)}(s)-\mathbf{x}^{(k)}(s)\right\| \leqslant 3\varepsilon^2 T+\int_0^s \left\|\mathbf{J}(\mathbf{x}^{(k-1)}(t))\right\| \left\|\left(\mathbf{y}^{(k)}(t)-\mathbf{x}^{(k)}(t)\right)\right\| \mathrm{d}t$$

for every $s \in [0,T]$, and by the Gronwall lemma we get the estimate

$$\left\|\mathbf{y}^{(k)}(s)-\mathbf{x}^{(k)}(s)\right\| \leqslant 3\varepsilon^2 T \mathrm{e}^{\int_0^s \|\mathbf{J}(\mathbf{x}^{(k-1)}(t))\| \,\mathrm{d}t} \leqslant 3\varepsilon^2 T \mathrm{e}^{Q},$$

for any $s \in [0,T]$, where

$$Q=\int_0^T \left\|\mathbf{J}\left(\mathbf{x}^{(k-1)}(t)\right)\right\| \mathrm{d}t<\infty,$$

because the sequence $\left(\mathbf{x}^{(k)}(t)\right)_{k=1}^{\infty}$ is bounded on the interval $[0,T]$ (this is the consequence of the first assertion). If we take $\varepsilon=\sqrt{\eta/(3T\mathrm{e}^{Q})}>0$ then we obtain immediately the assertion of the lemma. □

Corollary 4.6. *If the assumptions of Lemma* 4.4 *are satisfied then*

$$\lim_{k\to\infty}\left\|\mathbf{y}^{(k)}(t)-\mathbf{x}(t)\right\|=0$$

uniformly on $[0,T]$.

Theorem 4.7. *Assume that* $T>0$ *is given. Let* $\left(\mathbf{x}^{(l)}(t)\right)_{l=1}^{\infty}$ *be a sequence of solutions of the initial value problem* (4.12), (4.13), *corresponding to* $\alpha=(a_l,b_l,d_l)$ *which uniformly converges on the interval* $[0,T]$, *and let* $\mathbf{y}^{(k)}(t)$ *be the solution of the equation*

$$\dot{\mathbf{y}}=\mathbf{g}\left(\mathbf{x}^{(k-1)}\right)+\mathbf{J}\left(\mathbf{x}^{(k-1)}\right)\left(\mathbf{y}-\mathbf{x}^{(k-1)}\right)$$

on the interval $[0,T]$ *with the initial condition* $\mathbf{y}^{(k)}(0)=(I,0,a_k,b_k,d_k)^{\top}$.

Then

$$\lim_{k\to\infty}\left\|S\left(\mathbf{y}^{(k)}\right)-S\left(\mathbf{x}^{(k)}\right)\right\|=0$$

where $S(\mathbf{x})$ *is described in* (4.23).

P r o o f. Our assertion follows from Lemma 4.4 and from the fact that the terms $(x-r_i)^2$, $i=1,\ldots,L$, and $((I-x-y)-e_j)^2$, $j=1,\ldots,M$, occuring in (4.23) are continuous as functions of a vector $\mathbf{x}=(x,y,a,b,d)^{\top}$. □

R e m a r k 4.8. All the previous statements depend on the fact that we have at our disposal a uniformly convergent sequence $\mathbf{x}^{(k)}(t)$ of solutions of the initial value problem (4.12), (4.13).

5. Numerical results

For numerical computations we have seven data sets $M_1, \dots M_7$ of measured values of BSP in the blood (at times t_i) and in the bile (at times e_j) which are indicated in the following graphs by dots. Characterization of the measurement was given in the part describing the clinical data.

The first four cases $M_1, \dots, M_4$ give measurements for the same person. The BSP-test was done on the 6th, 25th, 26th and 27th day after cholecystectomy in this case. The initial amount of BSP was different, e.g. 125, 250 and 500 mg, respectively. Since the modelling system (1.1) is linear (its solutions form a linear space) the measured data can be modified to data which correspond to the uniform initial dose of BSP—250 mg for all cases.

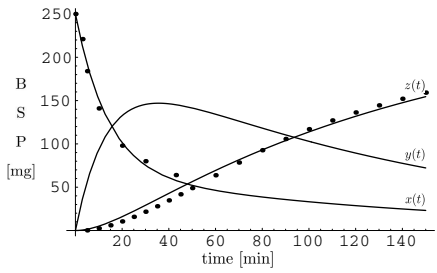
For obtaining numerical results the Mathematica software package was used. Three methods have been examined.

(1) FM—this method uses the analytical solution (2.1), (2.2) and the Mathematica command `FindMinimum` is applied to the function (3.1).
(2) QM—this is the Quasilinearization method described in the previous section.
(3) QFM—this method is a modification of QM. We do not solve the algebraic equations (4.9), the command `FindMinimum` for the function (4.21) is applied instead.

The numerical results, presenting the unknown parameters a, b, d, for the given cases are shown in the following tables. The corresponding graphs represent the solutions to (4.12), (4.13) for the values of the parameters a, b, d obtained by the Quasilinearization method.

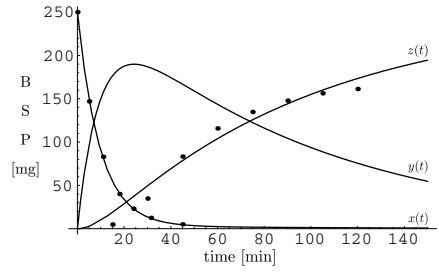
	a	b	d	steps
FM	0.054736	0.0152704	0.0093906	4
QFM	0.054736	0.0152704	0.0093906	11
Q	0.054736	0.0152704	0.0093906	13

Table 1. Numerical results for case M_1.



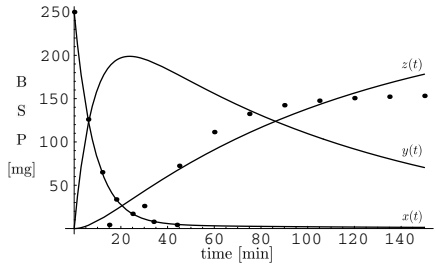
	a	b	d	steps
FM	0.1028669	0.0012472	0.0109183	3
QFM	0.1028669	0.0012472	0.0109183	8
Q	0.1028669	0.0012471	0.0109183	19

Table 2. Numerical results for case M_2.



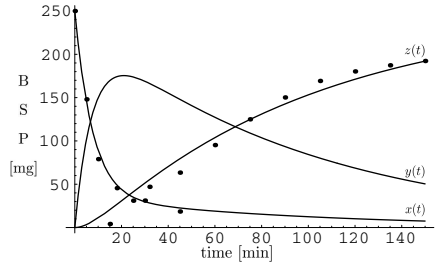
	a	b	d	steps
FM	0.1155239	0.0020142	0.009009	4
QFM	0.1155235	0.0020141	0.009009	11
Q	0.1155235	0.0020141	0.009009	17

Table 3. Numerical results for case M_3.



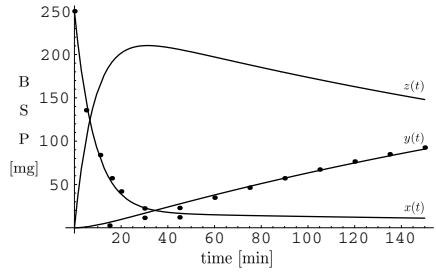
	a	b	d	steps
FM	0.1146878	0.0154462	0.0118261	3
QFM	0.1146877	0.0154462	0.0118261	8
Q	0.1146877	0.0154462	0.0118261	11

Table 4. Numerical results for case M_4.



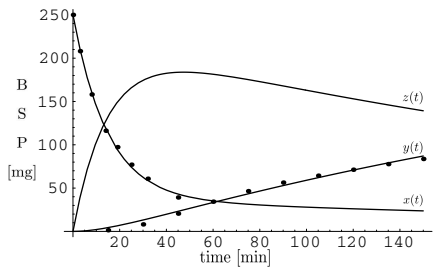
	a	b	d	steps
FM	0.1098251	0.0079839	0.0034339	6
QFM	0.1098253	0.0079840	0.0034339	10
Q	0.1098253	0.0079840	0.0034339	10

Table 5. Numerical results for case M_5.



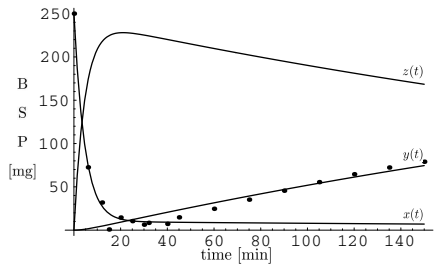
	a	b	d	steps
FM	0.0579301	0.0093114	0.0037127	5
QFM	0.0579301	0.0093114	0.0037127	9
Q	0.0579301	0.0093114	0.0037127	10

Table 6. Numerical results for case M_6.



	a	b	d	steps
FM	0.2070551	0.0085127	0.0025377	8
QFM	0.2070551	0.0085127	0.0025377	8
Q	0.2070550	0.0085127	0.0025377	9

Table 7. Numerical results for case M_7.



In the last column in Tables 1–7 we mention how many iterations were needed in the computation. We used the criterion (4.11) for $\varepsilon = 10^{-7}$. In the case when the analytical solution (FM method) is used, the least number of computing steps was needed. We must note that the number of steps for all methods depends on the initial choice α_1. For all cases in our tables the same starting value $\alpha_1 = (0.107, 0.004, 0.01)$ of the parameters was used.

According to the medical point of view [3], the satisfactory clinical status of the patient corresponds to the interval $[0.102, 0.116]$ of the parameter a. The meaning of values of parameters b, d for the characterization of liver function is not known at present and it should be interpreted on a larger sample of data.

References

[1] *R. Bellman, R. Roth*: Quasilinearization and the Identification Problem. World Scientific, Singapore, 1983.

[2] *P. Hartman*: Ordinary Differential Equations. S. M. Hartman, Baltimore, 1973.

[3] *E. Hrnčíř*: Personal notes. Unpublished.

[4] *R. Kalaba, K. Spingarn*: Control, Identification, and Input Optimization. Mathematical Concepts and Methods in Science and Engineering, Vol. 25. Plenum Press, New York-London, 1982.

[5] *J. M. Watt, A. Young*: An attempt to simulate the liver on a computer. Comput. J. *5* (1962), 221–227.

Author's address: *L. Čelechovská*, Mathematical Institute, Silesian University, Na Rybníčku 1, 746 01 Opava, Czech Republic, e-mail: `Lenka.Celechovska@math.slu.cz`.