INFORMATICA, 1995, Vol. 6, No. 1, 15–33

SOME ALGORITHMS IN MATHEMATICAL MODELLING OF DIABETES MELLITUS

Raimondas ČIEGIS

Institute of Mathematics and Informatics
2600 Vilnius, Akademijos St. 4, Lithuania

Mečys MEILŪNAS

Vilnius University, Computer Centre
2600 Vilnius, Saulėtekio St. 9, Lithuania

Abstract. This paper deals with mathematical modelling of diabetes mellitus. A recent classification of diabetes mellitus is given and a new approach in constructing a mathematical model of this disease is described. The aim of mathematical modelling is to help a patient and his doctor in management of diabetes. The algorithms for solving inverse problems of coefficients reconstruction are investigated. Results of computational experiments are given.

Key words: mathematical models, inverse problems, least-square algorithms, regularization methods, diabetes mellitus.

1. Diabetes mellitus and its treatment

1.1. Definition, role of the insulin and other hormones. Diabetes mellitus is one of the most widespread metabolic disorders. More than two percents of the Earth population suffer from various forms of this disease. The percent of ill people differs strongly in various ethnic groups (see Olson, 1989).

The following or a similar definition of diabetes mellitus is used as a rule: "Diabetes mellitus is a disease, caused by the absolute or relative insulin insufficiency and characterized by strong disorder of carbohydrate metabolism with hyperglycaemia and glycosuria and also by disorder of another kind of metabolism" (see Vorobjev, 1990).

Insulin is the hormone produced in pancreas by β cells of Langerhans islands. It is the main factor which controls the accumulation and metabolism

of energetic substratums arriving into organism. Insulin secretion after taking meals makes easier the reabsorption, utilization and accumulation of glucose, fats and amino acids. And on the contrary, the decrease of circulating insulin quantity causes the mobilization of endogenic energetic substratums and slows down the utilization of used meals. The action of insulin is concerned with all basic energetic substratums: carbohydrates, albumin and fats and it is realized mostly in tissues of liver, muscles and fat. In each of those tissues insulin has an anticatabolic and anabolic action, which intensify one another (see Felig *et al.*, 1982).

Glucagon and somatostatin are produced by the cells of another kind of Langerhaus islands. These hormones are also important for the analysis of diabetes mellitus. Glucagon is one of the most important hormonal antagonists of insulin, its action is opposite to insulin functions. Hormones of stomach-intestines, growth hormone (somatotrophin), stress hormones (adrenaline, noradrenaline) and other hormones are acting on the endogenical insulin secretion and on the metabolism. Many of them are acting on the substratums not directly, but only implicitly by activating the corresponding ferments (see Felig *et al.*, 1982).

It can be said in resume, that metabolism in humans organism is regulated by a big number of hormones and ferments with a different kind of action. The concentration of these hormones and ferments in blood plasma and it's changing in time, their interaction with substratums and between themselves have a determinant influence on the of metabolism. One of the most important function of the hormonal system is to keep up the concentration of glucose, lipids, albumens and products of their metabolism in blood plasma in the narrow interval. Diabetes mellitus is an example of the disorder of this function.

The classification of illness according to the etiology, the clinical features is important for diagnostics and treatment of diabetes. Various diabetes classifications are possible. One of them is recommended by the National Health Institute (USA). It proposes to distinguish five basic types of diabetes: spontaneous diabetes, which can be insulin dependent or non-insulin dependent, a second time diabetes, glucose tolerance disorder, diabetes of pregnant women (see Felig *et al.*, 1985).

Spontaneous insulin dependent (or first type diabetes) and spontaneous non-insulin dependent (or second type diabetes) are the mostly widespread types

of diabetes mellitus. Next we describe the character of clinical manifestations of first and second type diabetes.

The first type diabetes is characterized by the following features:

- usually people are becoming ill in youth (up to 40 years) – so sometimes it is called juvenile diabetes,
- the pancreas is producing too few endogenic insulin, or it is not producing it at all (absolute insufficiency of insulin),
- in the organism there exist the antibodies to the insulin producing cells,
- the beginning of the illness is spontaneous, the course is labile, the patient is inclined to ketosis, hypo- and hyperglycaemia,
- the insulin therapy is necessary for the compensation of diabetes.

The second type diabetes is characterized by these features:

- mostly people are becoming ill after 40 years old,
- as a rule, the pancreas is producing a sufficient quantity of the insulin, or even more than normally, but insulin's influence on metabolism is insufficient because of the organism tissues resistance to insulin (relative insufficiency of insulin),
- mostly patients are obese (about 80%),
- the beginning of illness usually is slow, stable, without ketosis,
- insulin injections mostly are not necessary for compensation, usually it is enough to choose appropriate diet and to use oral hypoglycemic agents.

Diabetes mellitus is dangerous for patient's health and life because of it's complications, which can be acute (e.g. diabetic coma, hypoglycaemia, lactoacidosis, hiperosmolarity) or chronic (e.g. angiopathy, retinopathy, nephropathy, neuropathy). All these complications can be described by the following scheme: they are functions of short or long time deviations of some substances concentration in blood plasma from the norm.

Glucose is the main of such substances (more precisely, it is blood sugar, which usually consists of glucose (85%), fructose and galactose). However, other substances such as the ketone bodies, lactic acid and others are also important. For example the increased concentration of ketone bodies and glycaemia can cause ketoacidosical (diabetical) coma, the increase of lactic acid (lactoacidosis), and significant decrease of glycaemia can cause hypoglycaemical coma.

Long lasting hyper-glycaemia is the main reason of chronic complications.

1.2. The purposes and methods of diabetes treatment.The aims of diabetical patients treatment are usually formulated in such a way:

1) normalization of carbohydrates, fats and albumen metabolism,

2) prophylactic of chronic complications,

3) ensuring a patient's normal psycho-social adaptations,

4) the prevention of hypoglycaemia and another acute complications.

The radical treatment of diabetes mellitus is possible by transplantation of β cells. Such kind of treatment can be used in the case of first type diabetes. However, this method is complicated and expensive, so it was applied only for few patients in the world.

Therefore, the practical aim of management of diabetes is to minimize the consequences of β cells insufficiency for the organism and to use various methods in order to achieve this goal.

The perspective method of treatment is the implantation of insulin pump with the open loop, which enables the regulation of insulin flow. But still it is not widely used method. Sometimes close loop type insulin injection systems with feedback relation are used in clinics. However, they demand frequent blood analysis and are too cumbersome, so in practice such systems can be used only for a short time and for a little number of patients. A construction of close loop type systems with implanted or noninvasive glycaemia indicator is not solved problem yet.

The most widespread method of diabetes mellitus treatment is subcutaneous injection of insulin 2–3 times a day in corporation with diet therapy and regulation of physical activity. In this case the aim of a patient and his physician is to choose and to coordinate such control parameters, which are in their disposition:

a) type and dose of injected insulin,

b) diet,

c) physical exercises.

The reestablishment of lost feedback can be realized by using measurements of glycaemia, glycosuria and a ketonuria, and the results of patients anamnesis.

We must notice, that the values of measurements mentioned above usually are not exact in practice. The measurements of glycaemia and glycosuria are

discrete in time, we can do only several measurements during a day. But the corresponding real processes are functions of the continuous time. Measurements of ketonuria usually are evaluated in gradually, but the real process is quantitative and continuous.

Hence we have the following situation: in the case of diabetes mellitus the majority of feedbacks, which support organism homeostasis, are lost or weakened. Usually we are dealing with the main parameter of homeostasis – glycaemia, and the main chain in the feedback – the concentration of insulin in blood plasma. We must emphasize at once, that the real mechanism of metabolism is much more complicated and the interaction of glucose and insulin is only one but important component. The main task in the treatment of diabetes mellitus is to reestablish this lost mechanism of metabolism. Since, it is impossible to achieve this completely in real conditions, so we can speak only about the partial reestablishment of this mechanism. The main method for solving this problem is the coordination of all external loadings, i.e., injected insulin, physical activity and diet.

Thus, a patient or/and his physician must solve the same problem every day: how to coordinate the regime of day and therapy (insulin, sometimes glucagon and peroral hyperglycaemizing drugs) in order to normalize the concentration of some substances, mainly glucose in blood plasma and in urine.

As a rule, the problem is solved in several stages. Initially, the type of the disease is find according to the classification given above. Here the main parameters are patient's age, height, weight, the data about glycaemia, glycosuria, anamnesis. Usually a patient is reckoned to first or second type diabetes. This is the first step of the identification of disease parameters. Further, according to the type of diabetes, common treatment schemes are applied. For example, in the case of first type diabetes the initial dose of insulin is chosen according to the used amount of carbohydrates (e.g. by the rule – 1 unit of insulin for 5 gr. of carbohydrates). In the case of second type diabetes a less caloric diet is intended for a patient in order to decrease his weight and subsequently to diminish the resistance of organism to insulin. Nutrition regime, therapy and physical activity are corrected according to glycaemia, glycosuria and other parameters.

Such work demands a large amount of data to be processed daily. Therefore, the implementation of computers in diabetes diagnosis and in diabetes

treatment is very desirable and has good perspective (see Berger and Rodbard, 1991).

2. Computers and mathematical modeling in Diabetes Mellitus.

2.1. Some general remarks. We can define the following main problems:

1. Data registration and graphical description. This can significantly lighten doctor's work, save his time, protect him from errors (see Piwernetz, 1991).

2. Expert systems. Anamnesis, classification, schemes of treatment, doctor's experience – these subjects can be formalized, so it is natural to create expert systems on computer basis in order to support treatment concerned decisions. This can diminish the size of routine work, or sometimes substitute it.

3. Mathematical models, developed to simulate effects of therapy and lifestyle alterations, to simulate insulin sensivity, to optimize some parameters of therapy and lifestyle factors in order to keep normoglycaemia and aglucouria.

2.2. Alternatives in mathematical modelling. Mostly glucose–insulin interaction is investigated in mathematical models. Of course, it is very important problem, but at the same time this problem is very complicated. Therefore, the investigator must choose between two alternatives:

– he can try to describe natural mechanism of metabolism regulation by elements of it's structure (substratums, hormones, ferments and so on) in order to emphasize their basic functions in the case of diabetes mellitus (see Švitra, 1989),

– the mathematical model can be used to describe the homeostatic functions of the organism, concerned with diabetes mellitus.

We think that the second approach can give better practical results. This approach can be realized by the following common scheme.

1. We must select a relevant phase space in order to determine the status of organism. The elements of this space should describe adequately these aspects of organism status, which are important for our problem. The illness (diabetes mellitus) is characterized by the deviation from norm of some substances concentrations in blood plasma. Glucose, ketonical bodies, lactic acid are the main such substances. Their concentration are called status variables, and model equations are written for these variables.

In the healthy organism buffer systems, which support normal concentra-

tion of these substances, work perfectly (for example, Fellig *et al.* (1982) describe buffer blood system for supporting the concentration of hydrogen iones). In the case of diabetes this buffer system is destroyed. Then the regulation of the concentration of some substance can be described by the following equation

$$\frac{dm}{dt} = k(m)m(t) + f(t),$$

where $m(t)$ denotes the concentration, $f(t)$ defines external forces, k is a given function, for example

$$k(m) = \begin{cases} -k_1(m - m_1), & \text{when } m \geqslant m_1, \\ 0, & \text{when } m_0 \leqslant m \leqslant m_1, \\ k_0(m_0 - m), & \text{when } m \leqslant m_0. \end{cases}$$

2. The disease complications are described by some functionals or operators (depending on the set of status variables of such complications) defined on status trajectory. For example, chronic hyperglycaemia gives a lot of complications (microangiopatia, neuropathy and so on), its trajectory for a long time interval is over the upper bound of normoglycaemia. Thus, it is naturally that the complication of illness is a consequence of status trajectory.

Let's investigate glycosuria as one of such consequences (it's not generally accepted to consider glycosuria as complication of diabetes). The quantity of sugar $g(t)$ extracted from urine during the fixed time interval $[0, t]$ can be defined by the integral

$$g(t) = \int_0^t q(G(\tau))\, G(\tau)\, d\tau,$$

where $G(\tau)$ is glycaemia at the time moment τ and $q(G(\tau))$ describes kidneys capability of sugar resorption or it's letting pass into urine. Coefficient $q(G)$ can be defined by the following formula

$$q(G) = \begin{cases} 0, & \text{when } G \leqslant G_a, \\ k_q(G - G_a), & \text{when } G_a \leqslant G \leqslant G_v, \\ k_q(G_v - G_a), & \text{when } G \geqslant G_v. \end{cases}$$

Now we will consider rather simplified mathematical model, written according to the assumptions given above. Let us suppose that organism status

is characterized by one variable – glycaemia and the buffer system is also depended on this variable. We assume that only one complication – glycosuria is taken into account.

Then we have:

$$\begin{aligned} \frac{dG}{dt} &= \Big[k(G) - q(G)\Big]G + f(G,t), \qquad 0 < t \leqslant T, \\ \frac{dg}{dt} &= q(g)G, \qquad 0 < t \leqslant T, \end{aligned} \tag{1}$$

where $G(0) = G_s$, $g(0) = 0$,

$$k(G) = \begin{cases} k_1(G) > 0, & \text{when } G < G_0, \\ 0, & \text{when } G_0 \leqslant G \leqslant G_1, \\ k_2(G) < 0, & \text{when } G > G_1, \end{cases}$$

$$(G) = \begin{cases} 0, & \text{when } G \leqslant G_2, \\ \dfrac{G - G_2}{G_3 - G_2}, & \text{when } G_2 < G < G_3, \\ 1, & \text{when } G > G_3. \end{cases}$$

We can formulate the following problems which are important in practice:

1) find $q(G)$ and $k(G)$ by using the obtained information on functions $g(t)$ and $G(t)$,

2) what minimal information about $g(t)$ and $G(t)$ is necessary and in what order it should be obtained for the reliable determination of $q(G)$ and $k(G)$.

In this paper we consider the problem of determining the function $q(G)$, only.

2.3. The model identification and related problems. We can distinguish two main cases:

1) there are no preliminary information about function $q(G)$,

2) a piecewise-linear approximation of $q(G)$ is used.

Firstly it is useful to discuss the initial data processing. At present there are no possibilities to measure $G(t)$ and $g(t)$ as functions of continuous argument for a big quantity of patients. Therefore, we are going to investigate more closely the situation which is typical for the clinical conditions. It is possible to measure glycaemia $G(t)$ and glycosuria $g(t)$ during the day at the separate time moments

$$\left\{ t_i^G \right\}_{i=1,\cdots,I} \qquad \text{and} \qquad \left\{ t_j^g \right\}_{j=1,\cdots,J}.$$

Usually I and J are less than 10. We also note, that data measurements, as a rule, are not precise and the measurements of glycosuria

$$g_i = \int_{t^g_{i-1}}^{t^g_i} q(G)G \, dt$$

are often made at such time moments, that there is no glycaemia's measuring data belonging to the same time interval $[t^g_{i-1}, t^g_i]$.

Therefore, the data about glycaemia and glycosuria gathered during 24 hours are insufficient to determine the functions $G(t)$ and $g(t)$ as continuous argument functions. We propose to use "averaged" observations of several days in order to get more accurate approximations of $G(t)$, $g(t)$. Let us assume that we have observations during several days

$$G_{i_k} = G(t^G_{i_k}), \qquad g_{j_k} = g(t^g_{j_k}),$$

where we use notation t_{ik} to mean the $i-$th measurement during the $k-$th day, $k = 1, \cdots, K$, $i_k = 1, \cdots, I_k$, $\quad j_k = 1, \cdots, J_k$.

Next we locate all the measurements in one day (24 hours) time interval $(0, T)$, where $T = 24\ h$ and divide time interval $[0, T]$ into N parts $\Delta t_n = t_n - t_{n-1}$, $\quad t_0 = 0$, $\quad t_N = T$. Assume that the sets of measuring moments

$$T^G_n = \left\{ t^G_{i_k,n} \right\} \qquad \text{and} \qquad T^g_n = \left\{ t^g_{j_n,n} \right\}$$

belong to the interval Δt_n. We denote the number of elements in these sets by M^G_n and M^g_n, respectively, and use the notation

$$t_{n-1/2} = \frac{t_n + t_{n-1}}{2}.$$

Now we define the values of the functions $G(t)$, $\quad g(t)$ at the time moments $t_{n-1/2}$ by

$$G(t_{n-1/2}) = \frac{1}{M^G_n} \sum_{i_k=1}^{M^G_n} G(t^G_{i_k,n}), \quad \text{if} \quad M^G_n > 0,$$

$$g(t_{n-1/2}) = \frac{1}{M^g_n} \sum_{j_k=1}^{M^g_n} g(t^g_{j_n,n}), \quad \text{if} \quad M^g_n > 0.$$

If $M_n^G = 0$ or $M_n^g = 0$ in some interval Δt_n, then we don't define the function for the corresponding time moment. We can use these values of functions $G(t)$, $g(t)$ as a piece-wise constant approximations in the time interval Δt_n.

Such "averaged" functions G and g haven't ordinary biomedical interpretation, because observations of several days are placed into one day (24 hours) time interval. However, if the assumptions given above are true during the whole period of observations, then functions G and g can be interpreted as hypothetical glycaemia and glycosuria for an "average" day.

Now we describe our first method for solving equation (1).

Method 1. In order to get a more accurate approximation we interpolate functions G and g by cubic splines. Let $[G_a,\ G_v]$ be the function's $G(t)$ variation interval. We divide it into L parts $[G_l,\ G_{l+1}]$ and denote

$$G_l^* = \frac{G_{l+1} + G_l}{2}, \qquad l = 0, 1, \cdots, L-1.$$

Function $q(G)$ is approximated by a stepwise function

$$q_l(G) = q(G_l^*), \quad \text{if} \quad G_l \leqslant G \leqslant G_{l+1}. \tag{2}$$

Next we cover the interval $[0, T]$ by the set of subintervals $[t_{p-1}, t_p\ ]$.

Equation (1) is replaced by the system of algebraic equations

$$\sum_{l_p=1}^{L_p} q(G_{l_p}^*) G_{l_p} = g_p - g_{p-1}, \qquad p = 1, \cdots, P. \tag{3}$$

It's natural to assume, that $P \gg L$. Therefore, we have obtained a system of P equations with L unknown variables, where the number of equations is much greater than number of unknown variables. We use the least squares method for solving this problem, i.e., the system of linear equations

$$Ax = b$$

is replaced by the minimization problem of the function $F(x) = (Ax - b, Ax - b)$.

Method 2. Let us formulate the inverse problem for the equation (1). We know the values of the functions $g(t)$, $G(t)$ at the fixed time moments

$$(g(t_k), G(t_k)) \qquad 0 \leqslant t_k < t_{k+1} \leqslant T, \quad k = 0, 1, \cdots, K-1.$$

We want to find such function $q(G)$, which minimizes the functional

$$\Phi_q = \sum_{k=0}^{k-1} (q(G_k)G_k - f_k)^2, \tag{5}$$

where f_k denotes a suitable approximation of $\frac{dg(t_k)}{dt}$. In order to develop numerical methods for solving this minimization problem we must investigate two main problems.

The first problem deals with the numerical differentiation. There are given values of the function $g(t_k)$ at the time moments t_k and we need to calculate the derivative $g'(t)$. It is ill-posed mathematical problem because exact values of $g(t_k)$ are not known and measurement errors are introduced. In order to get stable numerical differentiation method we must use some regularization algorithm. The second problem deals with the evaluation of the function $q(G)$. It is well known that the identification of coefficients of a differential equation is also ill-posed mathematical problem. Therefore, we must use the regularization principle in this case, also.

Next we consider both problems in detail.

Step 1. Numerical differentiation. At first we will explain briefly why the numerical differentiation is ill-posed mathematical problem. Suppose, that we need to calculate the derivative of the function $g(t)$ when only values of the function $g(t)$ at the time moments $\{t_k\}$ are known, and, additionally, we assume that these values are measured with error:

$$\tilde{g}(t_k) = g(t_k) + \delta_k \ , \quad k = 1, 2, \cdots, K.$$

We know that errors δ_k are bounded by some constant δ

$$|\delta_k| \leqslant \delta, \quad k = 1, 2, \cdots, K,$$

where δ is defined by the precision of the measuring device.

Let us consider the simplest finite difference method of numerical differentiation:

$$D_\tau g = \frac{g(t_k) - g(t_{k-1})}{t_k - t_{k-1}}. \tag{6}$$

We will estimate the global error of this formula. Let us denote $\tau_k = t_k - t_{k-1}$. The Taylor expansion of the g(t) gives

$$D_\tau g = g'(t_k) - \frac{\tau}{2} g''(t_k + \Theta\tau_k) + \frac{\delta_k - \delta_{k-1}}{\tau_k}. \tag{7}$$

Then the quantity $\Psi_k^{(1)} = 0.5\tau_k g''(t_k + \Theta\tau_k)$ is the approximation error of the finite difference method, it converges to zero linearly as $\tau \to 0$:

$$|\Psi_k^{(1)}| \leqslant C_2\tau_k, \tag{8}$$

where C_2 is a constant such that $|g''(t)| \leqslant C_2$. The second part of the global error depends on data errors, it can be estimated as

$$|\Psi_k^{(2)}| = \left|\frac{\delta_k - \delta_{k-1}}{\tau_k}\right| \leqslant \frac{2\delta}{\tau_k}.$$

Therefore $\Psi_k^{(2)} \to \infty$ as $\tau_k \to 0$. We see that numerical differentiation is ill-posed mathematical problem.

We will use two simple regularization algorithms to solve the problem of numerical differentiation.

ALGORITHM 1. This method is useful when the set of data is sufficiently large. Suppose that the approximation error is estimated by

$$|\Psi_k^{(1)}| \leqslant c_p\tau^p.$$

Then we obtain the optimal value of the parameter τ by minimizing the global error, it is given by formula

$$\tau_0 = \left(\frac{2\delta}{pc_p}\right)^{1/(p+1)}. \tag{9}$$

We see that the algorithm is regularized by connecting the value of the discretization parameter τ with the estimation of data error.

To give an illustration of this method we present numerical results for the model problem with $g(t) = \exp(t)$, $t_i = 1$. The data errors are introduced by computer arithmetics. We made calculations on PC – 386 computer with single

and double precision. In Table 1 global errors are given for the method of numerical differentiation (6). The second and fourth raws of the table contain single precision global errors and double precision global errors, respectively. The values of the discrete parameter τ are given in the first and third raws of the table.

Table 1. Global errors of the numerical differentiation method (6)

h	0.5(−0.2)	0.1(−0.2)	0.5(−0.3)	0.1(−03)	0.5(−04)
Ψ	0.682(−0.2)	0.144(−0.2)	0.845(−03)	0.962(−03)	0.172(−02)
h	0.1(−06)	0.5(−07)	0.1(−07)	0.5(−08)	0.1(−08)
Ψ	0.137(−06)	0.709(−07)	0.280(−07)	0.357(−07)	0.146(−06)

ALGORITHM 2. (Variational regularization method). This general regularization method is developed by A. Tichonov (see Tichonov and Arsenin, 1986). The calculation of the derivative $z = \tilde{g}'(t)$ is equivalent to solving the following integral equation

$$\int_0^1 k(t,s)z(s)\,ds = \tilde{g}(t), \tag{10}$$

where

$$k(t,s) = \begin{cases} 1, & \text{if } 0 \leqslant s \leqslant t, \\ 0, & \text{if } t < s \leqslant 1. \end{cases}$$

By using the Tichonov regularization principle we replace the integral equation (10) by the integro-differential problem (see Tichonov and Arsenin, 1986)

$$\int_0^1 K(s,x)z(x)\,dx + \alpha\big(z(s) - p(s)z''(s)\big) = \int_0^1 k(t,s)\tilde{g}(t)\,dt,$$

$$z'(0) = 0, \quad z'(1) = 0,$$

where we define the auxiliary function $K(s,x)$ by

$$K(s,x) = \int_0^1 k(t,s)\, k(t,x)\, dt = \begin{cases} 1-x, & \text{if} \quad 0 \leqslant s \leqslant x, \\ 1-s, & \text{if} \quad 0 \leqslant x \leqslant s, \end{cases}$$

and $p(s)$ is a given function such that $p(s) \geqslant p_0 > 0$. Therefore $z(t)$ satisfies the following equation

$$\int_0^1 (1-x)z(x)\, dx + (1-s)\int_0^s z(x)\, dx + \alpha\{z(s) - p(s)z''(s)\} = \int_0^1 k(t,s)\tilde{g}(t)\, dt. \tag{11}$$

The regularization parameter α can be defined by considering a residual of the integral equation (10). After discretization we have a system of linear algebraic equations with a symmetrical matrix.

Step 2. Evaluation of the function $q(G)$. We consider a piecewise-linear function

$$y(x,a,b,c) = \begin{cases} 0, & \text{if} \quad x \leqslant a, \\ c(x-a)/(b-a), & \text{if} \quad a \leqslant x \leqslant b, \\ c, & \text{if} \quad x \geqslant b, \end{cases} \tag{12}$$

where a, b, c are unknown parameters such that $b > a > 0, \quad c > 0$. The values of the function $y(x)$ are measured for a set of points $\{x_i\}$

$$y_i = y(x_i, a, b, c), \qquad i = 1, 2, , \cdots, n.$$

Let p be a vector of parameters $p = \left(p_1, p_2, p_3\right)^T$, where $p_1 = a, p_2 = b, p_3 = c$. We can find parameters p by minimizing the function

$$\Phi(p) = \sum_{i=1}^{n} \left(y(x_i, p) - y_i\right)^2 = |Z(p)|^2, \tag{13}$$

where $Z(p)$ is a vector of residuals

$$Z(p) = (z_1, z_2, \cdots, z_n), \qquad z_i = y(x_i, p) - y_i.$$

We will consider three methods which are used to solve minimization problem (13):

a) the gradient method,

b) Gauss-Newton method,

c) a combination of these methods.

The gradient method. A new approximation of p is defined by the equation

$$p^{s+1} = p^s - \tau_s \frac{\partial \Phi(p^s)}{\partial p}, \tag{14}$$

where

$$\frac{\partial \Phi(p)}{\partial p} = \left(\frac{\partial \Phi(p)}{\partial p_j}\right)^T, \qquad j = 1,2,3.$$

The parameter τ_s is defined in such a way that

$$\Phi\left(p^{s+1}\right) < \Phi\left(p^s\right).$$

In addition we require that the following conditions:

$$b^{s+1} > a^{s+1}, \qquad c^{s+1} > 0$$

would be satisfied.

The Gauss-Newton method. This method is constructed by using the linearization of the function $\Phi(p)$ in a neighbourhood of the point p^s :

$$\Phi(p) = \Phi(p^s + \delta p^s) = |Z(p^s + \delta p^s)|^2 \approx |Z(p^s) + \frac{\partial y(p^s)}{\partial p}\delta p^s|^2, \tag{15}$$

where $\dfrac{\partial y(p)}{\partial p}$ is a Jacobian $n \times 3$ matrix. From (15) we obtain that

$$\Phi(p) \simeq |Z(p^s)|^2 + 2\left(\delta p^s\right)^T \left(\frac{\partial y(p^s)}{\partial p}\right)^T Z(p^s) +$$

$$\left(\delta p^s\right)^T \left(\frac{\partial y(p^s)}{\partial p}\right)^T \frac{\partial y(p^s)}{\partial p}\delta p^s.$$

We can find the minimum point of quadratic function exactly by solving the 3×3 linear system

$$\left(\frac{\partial y(p^s)}{\partial p}\right)^T \left(\frac{\partial y(p^s)}{\partial p}\right) \delta p^s = -\left(\frac{\partial y(p^s)}{\partial p}\right)^T Z(p^s) = -\frac{1}{2}\frac{\partial \Phi(p^s)}{\partial p}. \tag{16}$$

It is possible to generalize this method by introducing two parameters α_s, τ_s:

$$\left[(1-\alpha_s)\left(\frac{\partial y(p^s)}{\partial p}\right)^T\left(\frac{\partial y(p^s)}{\partial p}\right)+\alpha_s E\right]\delta p^s=-\tau_s\frac{\partial\Phi(p^s)}{\partial p}. \tag{17}$$

The parameters α_s, τ_s are chosen so that

$$\Phi(p^{s+1}) < \Phi(p^s).$$

We start with $\alpha_s = 0$, then enlarge it, if the Gauss-Newton method matrix is singular. Further, provided that $\alpha_s = 0$ for s sufficiently large, the method has a quadratic rate of convergence.

REMARK. Assuming $\alpha_s = 1$ we obtain the gradient method.

Method 3. We propose one more iterative process. Let us introduce new parameters in the definition of function $y(x,p)$:

$$y(x,k,A,c)=\begin{cases}0, & \text{if } x<a,\\ kx+A, & \text{if } a\leqslant x\leqslant b,\\ c, & \text{if } x>b.\end{cases} \tag{18}$$

These parameters are connected with the previous parameters a, b, c by the relations:

$$ka+A=0, \qquad kb+A=c. \tag{19}$$

We have from equations (19) that

$$a=-A/k, \qquad b=(c-A)/k. \tag{20}$$

The algorithm is given below. Assuming that the approximation $(a^s,\ b^s)$ is known, we find out the parameters k^s, A^s, c^s from the following minimization problem:

$$\Phi(p)=\sum_{i=1}^{n}\left(y^s(x_i,k,A,c)-y_i\right)^2\to\min_{k,A,C}. \tag{21}$$

It is easy to see, that this problem defines regression lines in the areas

$$Q_2=\left\{x_i:\ a^s\leqslant x_i\leqslant b^s\right\}, Q_3=\left\{x_i:\ x_i\geqslant b^s\right\}.$$

Therefore the parameter c^s is derived from the formula

$$c^s = \sum_{x_i \in Q_3^s} y_i \; / \sum_{x_i \in Q_3^s} 1,$$

and $\{k^s,\ A^s\}$ are the solution of the linear equation system:

$$\begin{aligned} \Big(\sum_{x_i \in Q_2^s} x_i^2 \Big) k^s + \Big(\sum_{x_i \in Q_2^s} x_i \Big) A^s &= \sum_{x_i \in Q_2^s} x_i y_i, \\ \Big(\sum_{x_i \in Q_2^s} x_i \Big) k^s + \Big(\sum_{x_i \in Q_2^s} 1 \Big) A^s &= \sum_{x_i \in Q_2^s} y_i. \end{aligned} \tag{22}$$

The new values of the parameters a, b are defined by the formulas

$$a^{s+1} = a^s - \tau_s (A^s/k^s + a^s), \qquad b^{s+1} = b^s + \tau_s \left((c^s - A^s)/k^s - b^s \right), \tag{23}$$

where τ_s is calculated by searching in this direction for an approximate minimizer of Φ:

$$\Phi\left(p^{s+1}\right) < \Phi\left(p^s\right),$$

and demanding that conditions $a^s < b^s$ would be satisfied.

We have carried out numerical calculations with all three methods. In Table 2 we present some numerical results. The data error was introduced by function $\delta \cos(\pi x)$. N denotes the number of measurements. Table 2 contains the number of iterations needed by three methods in order to solve minimization problem (13) with the accuracy $\varepsilon = 0.001$.

Table 2. Number of iterations for three methods

δ	N	Method 1	Method 2	Method 3
0	35	63	4	5
0.05	30	47	5	6

These numerical algorihms are also investigated by Čiegis, Meilūnas and Juknevičienė (1994).

Acknowledgements. We are indebted to Genė Kairytė from MII for her support in the development of numerical algorithms and computer programs. We would like to thank our colleques in Vilnius University Computer Center for discussions and for the help in numerous numerical experiments, particularly Danguolė Juknevičienė and Natasha Kosareva. M. Meilūnas also would like to thank Edita Janulionytė and Vaidotas Urbanavičius from Medical Department of Vilnius University for discussions and suggestions which were very helpfull.

REFERENCES

Berger, M., and D.Rodbard (1991). Toward the implementation of computers in diabetes mellitus. *Diabetes, Utrition & Metabolism,* **4**(1), 77–87.

Čiegis, R., M.Meilūnas and D.Juknevičienė. (1994). On the identification algorihms in the renal threshald mathematical model. In *Proceedings of the Third Seminar on Computational Mathematics.* Vilnius. pp. 28–33.

Felig, Ph., J.D.Baxter, A.E.Brodus and L.A.Frohman. (1982). *Endocrinology and Metabolism.* McGraw-Hill International Book Company, New York. 416pp.

Olson, O.Ch. (1989). *Diagnosis and Management of Diabetes Mellitus.* Raven press, New York. 293pp.

Piwernetz, K. (1991). Diabetes self care and long-term monitoring. *Diabetes, Nutrition & Metabolism,* **4**(1), 87–93.

Švitra, D. (1989). *Dynamics of Physiological Systems.* Mokslas, Vilnius. 170pp. (in Russian).

Tichonov, A.N., and V.Ya.Arsenin (1986). *Methods of Solving Noncorrect Mathematical Problems.* Nauka, Moscow. 288pp. (in Russian).

Vorobjev, A.I. (Ed) (1990). *Manual of General Practicioner.* Medicina, Moscow. 432pp. (in Russian).

Received April 1995

R. Čiegis has graduated from the Vilnius University (Faculty of Mathematics) in 1982, received the Degree of Candidate of Physical and Mathematical Sciences from the Institute of Mathematics of Byelorussian Academy of Sciences in 1985 and the Degree of Habil. Doctor of Mathematics from the Institute of Mathematics and Informatics, Vilnius in 1993. He is a head of the Mathematical Modelling Sector, Institute of Mathematics and Informatics. R. Čiegis is also a Professor of Kaunas Vytautas Magnus University and Vilnius Technical University. His reseach interests include numerical methods for nonlinear PDE, adaptive difference schemes, parallel numerical algorithms, mathematical modelling in optics, biophysics, ecology.

M. Meilūnas was born in 1950. He graduated from the Department of Mathematics of the Vilnius University in 1974. He works at the Vilnius University Computer Center. His research interest include mathematical modelling in biosciences (diabetology, cancer reserch) and numerical mathematics.

APIE DIABETO MATEMATINIO MODELIAVIMO ALGORITMUS

Raimondas ČIEGIS, Mečys MEILŪNAS

Nagrinėjama svarbi matematinio modeliavimo problema – diferencialinių lygčių koeficientų identifikavimo skaitinių algoritmų sudarymas medicininiams modeliams. Pasirinktas toks diabeto matematinio modelio sudarymo būdas, kai nenagrinėjami sudėtingi pirminiai šią ligą sukeliantys procesai, o apsiribojama tik apibendrinta svarbiausių parametrų analize. Tai leidžia sudaryti matematinį konkretaus ligonio modelį ir, pasinaudojant visose ligoninėse gaunamais laboratoriniais tyrimų duomenimis, identifikuoti modelio parametrus. Išnagrinėti skaitiniai nekorektiškų matematikos uždavinių: skaitinio diferencijavimo ir atvirkštinio diferencialinės lygties koeficientų radimo, sprendimo metodai. Teorinė analizė iliustruojama skaičiavimo eksperimento rezultatais.