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THEORETICAL AND MATHEMATICAL PHYSICS

New Data Processing Technique Based on the Optimal Control Theory

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Abstract—The problem of choosing the best set of parameters for a given mathematical model that adequately describes independent experimental data is formulated in terms of the optimal control theory. The sum of squares of discrepancies between experimental data and their analogues calculated within the framework of a given mathematical model of a process is minimized. A solution to the problem is found, and conditions for optimally choosing the parameters of the mathematical model are established. The search algorithm is generalized for the case where a penalty function is present, and an efficient way of including inequality constraints is suggested. The algorithm was tested by finding the thermal conductivity of single crystals (Ioffe–Ioffe classical experiment), thermal diffusivity of a thin plate, and parameters of gene expression during the fruit fly (*Drosophila melanogaster*) embryo evolution. © *2003 MAIK "Nauka/Interperiodica".*

INTRODUCTION

Let a boundary-value problem for a set of equations with given differential operator and boundary (initial) conditions be the mathematical model of a process. In check experiments, the coefficients of the equations, as well as dissimilar terms in the equations and boundary conditions, are unknown (or partially known) and have to be found in such a way that the model describes adequately experimental data obtained independently. Usually, a set of boundary-value problem parameters (coefficients of equations, source functions, etc.) that best fits experimental data under given conditions is sought in this case. If mere interpolation fails, the problem may be solved in terms of the optimal control theory. The development of such an approach to experimental data processing is the aim of this work.

To find the phenomenological parameters of a model, one may apply the least-squares method to fit experimental data. Then, in terms of the optimal control theory, a model quality functional to be minimized is the sum of the squares of deviations of experimental data from values calculated independently within the framework of this mathematical model. The deviations are summed at times they were determined in experiments. Such a functional may have several local minima and, if necessary, a penalty function. Also, inequality constraints may be imposed on some of the problem parameters.

In the simplest statement, this problem was briefly considered in [1]. In the work cited, an associated algorithm was described and generalized for the case with a penalty function and an efficient way of taking into account inequality constraints was suggested.

1. STATEMENT OF THE PROBLEM

Suppose we know the values of some vector function $y(t_i) = (y_0(t_i), \ldots, y_{K-1}(t_i))^T$ that characterizes the state of a system at different times. The superscript T hereafter means transposition; $i = 1, \ldots, J$, where J is the total number of time instants at which independent experimental data were obtained; and K is the number of state variables for a system studied. We assume that a system of first-order differential equations in the independent variable t together with a boundary condition is given and that this system depends on the vector of parameters $q = (q_0, \ldots, q_{I-1})^T$, where I is the number of parameters:

$$\frac{\partial v}{\partial t} = f(v, q); \quad v(0) = v_0. \tag{1}$$

This system describes the behavior of a physical system in experiments. The left side of (1) is the vector of dimension K, which is composed of time derivatives of the function $v(t, q)$ (state variables), and the right side of (1) is the vector function $f(v, q)$. If necessary, a penalty function $P(q)$ can be introduced into the problem.

Let us introduce a set of indices of parameters I_l on which inequality constraints

$$q_i^{\text{low}} \le q_i \le q_i^{\text{up}}, \quad i \in I_l \subset I \tag{2}$$

are imposed.

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Optimal control in this case consists in choosing parameters such that the quality functional (a measure of deviation of measured data from those calculated in terms of an independent model for a physical process)

$$F(v, q) = \sum_{i=1}^{J} (v(t_i, q) - y(t_i))^T (v(t_i, q) - y(t_i)) + P(q) = \varphi(v_1, \ldots, v_J) + P(q), \quad v_i = v(t_i, q) \tag{3}$$

is minimized.

Note that many problems of mathematical physics that are stated in the form of higher order differential equations can be reduced to the normal form, i.e., to a system of first-order equations with additional parametric variables (Pfaffian special system) [2]. Therefore, the selection of system (1) as the basic set of the problem stated is justified.

Finding the minimum of the quality functional necessitates the derivation of first-order stationary conditions. For system (1), which is written in general form, they are conveniently found with the Lagrange method of multipliers. In this case, however, one must consider an extended quality functional that includes inequalities (2), which impose restrictions on the control parameters. To this end, inequalities (2) must be transformed into equivalent equalities.

2. NECESSARY CONDITIONS FOR MINIMUM

To derive necessary conditions for stationarity (optimality) for quality functional (3), it is necessary to introduce additional controls u_i for which one can write equivalent equalities. Since the choice of these equalities is ambiguous, we will consider algebraic and trigonometric transformations of the inequalities into equivalent equalities.

(1) Algebraic transformation of the restricting inequalities. Let us replace inequalities (2) with the algebraic equalities [3]

$$\xi_i = (q_i - q_i^{\text{low}})(q_i^{\text{up}} - q_i) - u_i^2 = 0. \tag{4}$$

It is obvious that the condition $u_i = 0$ is satisfied if the initial parameter takes on either of the two preset extreme values, $q_i = q_i^{\text{low}}$ or $q_i = q_i^{\text{up}}$, and any $u_i \neq 0$ corresponds to an intermediate value of the control parameter: $q_i^{\text{low}} < q_i < q_i^{\text{up}}$.

Next, we introduce a vector function $\psi(t)$ of Lagrangean multipliers to include Eqs. (1) into the functional and a necessary number μ_i of Lagrangean multipliers to take into account the inequality constraints, which were transformed into (4). The extended functional of the problem can now be written in the form

$$L = \varphi(v_1, \ldots, v_J) + \sum_{i=0}^{J-1} \int_{t_i}^{t_{i+1}} \psi^T(t)\left(-\frac{\partial v}{\partial t} + f(v, q)\right)dt + \mu^T \xi + P(q), \tag{5}$$

where the vectors $\mu = \{\mu_i\}$ and $u = \{u_i\}$, as well as the vector function $\xi(q, u) = \{\xi_i(q, u)\}$, are introduced for all $i \in I_l$.

Thus, the restrictions are involved in the extended functional and it reaches an extremum simultaneously with (3). This allows us to use the standard procedure for deriving the stationarity conditions.

Having calculated the first variation of the quality functional

$$\delta F = \frac{\partial \varphi}{\partial v_1}\delta v_1 + \ldots + \frac{\partial \varphi}{\partial v_J}\delta v_J + \left(\frac{\partial P}{\partial q}\right)^T \delta q, \tag{6}$$

which is a measure of discrepancy between measured and calculated data, and the first variation of differential constraints

$$-\frac{\partial \delta v}{\partial t} + \frac{\partial f}{\partial v}\delta v + \frac{\partial f}{\partial q}\delta q = 0, \tag{7}$$

which are the equations of model (1), we can write the first variation of the Lagrangean function as

$$\delta L = \sum_{i=1}^{J} \frac{\partial \varphi}{\partial v_i}\delta v_i + \sum_{i=0}^{J-1} \int_{t_i}^{t_{i+1}} \psi^T(t)\left(-\frac{\partial \delta v}{\partial t} + \frac{\partial f}{\partial v}\delta v + \frac{\partial f}{\partial q}\delta q\right)dt + \mu^T\left(\frac{\partial \xi}{\partial q}\delta q + \frac{\partial \xi}{\partial u}\delta u\right) + \left(\frac{\partial P}{\partial q}\right)^T \delta q, \tag{8}$$

where $\partial P/\partial q$ are the components of the vector $\partial P/\partial q_i$.

Integrating (8) by parts yields

$$\delta L = \sum_{i=1}^{J} \frac{\partial \varphi}{\partial v_i}\delta v_i + \sum_{i=0}^{J-1} [\psi^T(t_i + 0)\delta v_i - \psi^T(t_{i+1} - 0)\delta v_{i+1}] + \left(\frac{\partial P}{\partial q}\right)^T \delta q + \sum_{i=0}^{J-1} \int_{t_i}^{t_{i+1}} \left[\left(\psi^T \frac{\partial f}{\partial v} + \frac{\partial \psi^T}{\partial t}\right)\delta v + \psi^T \frac{\partial f}{\partial q}\delta q\right]dt + \mu^T\left(\frac{\partial \xi}{\partial q}\delta q + \frac{\partial \xi}{\partial u}\delta u\right). \tag{9}$$

Here, $\psi(t_i + 0)$ and $\psi(t_{i+1} - 0)$ are the right- and left-hand limits of the Lagrangean multipliers $\psi(t)$ at intermediate points where experimental data are available; therefore, the values of Lagrangean multipliers (the function $\psi(t)$) vary in steps.

Below are a set of first-order minimum conditions for the quality functional [4] that use the stationarity

condition $\delta L = 0$:

$$\frac{\partial f}{\partial v}\psi + \frac{\partial \psi}{\partial t} = 0 \ \forall\ t \in [t_i, t_{i+1}); \tag{10}$$

$$\frac{\partial \varphi}{\partial v_i} - \psi(t_i - 0) + \psi(t_i + 0) = 0, \quad i = 1, \ldots, (J-1); \tag{11}$$

$$\frac{\partial \varphi}{\partial v_J} - \psi(t_J) = 0; \tag{12}$$

$$\mu_i u_i = 0, \quad i \in I_l. \tag{13}$$

This set of equations solves the problem of minimizing the discrepancy between experimental data and data calculated from a solution to the boundary-value problem.

Thus, the stationarity condition can be recast in the form of a vector equality for the Lagrange function gradient ζ:

$$\zeta(v, q) \equiv \int_{t_0}^{t_J} \psi^T \frac{\partial f}{\partial q} dt + \frac{\partial P}{\partial q} + \mu^T \frac{\partial \xi}{\partial q} = 0. \tag{14}$$

(2) Numerical solution algorithm. Let a set of I parameters q be given, a physical process be described by system (1), and it be necessary to find the coefficients of the equations such that the discrepancy between a solution to the model mathematical problem and measurements is minimal at each point of a given interval. Then, a solution algorithm for the problem stated by (1)–(3) consists of the following steps.

(1) Equation (1) is integrated.

(2) Equation (10) is integrated in reverse order, i.e., from t_J to t_0, in view of initial condition (12) and conditions (11) at those intermediate points where experimental data are available.

(3) The parameter gradient $\zeta^k = \zeta(v^k, q^k)$ is calculated by formula (14).

(4) Condition (13) for Lagrangean multipliers that correspond to algebraic constraints for additional controls u_i is satisfied as follows. If a parameter q_i in (2) meets the strict inequality, $\mu_i = 0$; otherwise, $u_i = 0$ and μ_i is selected so that a new value of the parameter q_i is allowable.

(5) New values of parameters q^{k+1} are found by the formula

$$q^{k+1} = q^k - \alpha^k \zeta^k, \tag{15}$$

where k is the number of iterations and α^k is a parameter selected so that functional (3) diminishes at each step.

Steps 1–5 are repeated until a desired calculation accuracy is achieved, for example, until the value of the functional becomes less than a preset value. A vector of parameters q^N obtained at the last step specifies a solution to the problem.

(3) Trigonometric transformation of constraints. The commonly used procedure in the optimal control theory is the replacement of control parameters q_i for which inequality constraints (2) are imposed by new controls u_i by means of trigonometric relationships, for example,

$$u_i = \alpha_i + \beta_i \sin(\gamma q_i), \tag{16}$$

where the factor γ is taken so as to improve divergence during numerical experiments and the constant α and β are determined from the upper and lower limits of the initial controls:

$$\alpha_i = (q_i^{\text{up}} + q_i^{\text{low}})/2; \quad \beta_i = (q_i^{\text{up}} - q_i^{\text{low}})/2.$$

Clearly, such a transformation is not unique; therefore, it seems reasonable to consider another finite representation:

$$u_i = \alpha_i + \beta_i \tanh(\gamma q_i). \tag{17}$$

The above transformations are applied only to those q_i that must satisfy conditions (2). Thus, instead of (1), we obtain upon rearrangements

$$\frac{\partial v}{\partial t} = \bar{f}(v, \bar{q}, u), \tag{18}$$

where $\bar{q} = \{q_i\}$ for $i \notin I_l$ and $u = \{u_i\}$ for $i \in I_l$.

Designating $\{u_i\}$ as $\{q_i\}$, where $i \in I_l$, we can write (18) in the form of (1), where $q = \{q_i\}$ and $i = 0, 1, \ldots, I-1$.

To derive necessary minimum conditions for the discrepancy functional, we write the Lagrangean

$$L = \varphi(v_1, \ldots, v_J) + \sum_{i=0}^{J-1} \int_{t_i}^{t_{i+1}} \psi^T(t)\left(-\frac{\partial v}{\partial t} + f(v, q)\right)dt + P(q), \tag{19}$$

where $\psi(t)$ is, as before, the vector function of Lagrangean multipliers.

Now, there is no need for additional multipliers that include inequality constraints into the extended functional, since they are involved in the equations.

After integrating (19) by parts, the standard derivation of necessary conditions for minimum leads us to a formula for the first variation of the Lagrangean:

$$\delta L = \sum_{i=1}^{J} \frac{\partial \varphi}{\partial v_i}\delta v_i + \sum_{i=0}^{J-1} [\psi^T(t_i + 0)\delta v_i - \psi^T(t_{i+1} - 0)\delta v_{i+1}] + \sum_{i=0}^{J-1} \int_{t_i}^{t_{i+1}} \left[\left(\psi^T \frac{\partial f}{\partial v} + \frac{\partial \psi}{\partial t}\right)\delta v + \psi^T \frac{\partial f}{\partial q}\delta q\right]dt + \left(\frac{\partial P}{\partial q}\right)^T \delta q. \tag{20}$$

By virtue of the stationarity condition $\delta L = 0$, the necessary conditions for minimum have the form

$$\frac{\partial f}{\partial v}\psi + \frac{\partial \psi}{\partial t} = 0 \quad \forall\ t \in [t_i, t_{i+1}); \tag{21}$$

$$\frac{\partial \varphi}{\partial v_i} - \psi(t_i - 0) + \psi(t_i + 0) = 0, \quad i = 1, \ldots, (J-1); \tag{22}$$

$$\frac{\partial \varphi}{\partial v_J} - \psi(t_J) = 0. \tag{23}$$

Thus, the stationarity conditions may be recast as the vector equality

$$\zeta(v, q) = 0, \tag{24}$$

where ζ is the Lagrangean gradient:

$$\zeta(v, q) = \int_{t_0}^{t_J} \psi^T \frac{\partial f}{\partial q} dt + \frac{\partial P}{\partial q}. \tag{25}$$

(4) Numerical solution algorithm for the trigonometric transformation of the constraints. Let a set of I parameters q be given, a physical process be described by system (1), and it be necessary to find the coefficients of the equations such that the discrepancy between a solution to the model mathematical problem and independent measurements is minimal at each point of a given interval. Then, a solution algorithm for the problem stated by (1)–(3) consists of the following steps.

(1) System (1) is integrated with a desired accuracy.

(2) Conjugate system (21) is integrated in reverse order, i.e., from t_J to t_0, in view of (22) and (23).

(3) The parameter gradient $\zeta^k = \zeta(v^k, q^k)$ is calculated by formula (24).

(4) New values of parameters q^{k+1} are found by the formula

$$q^{k+1} = q^k - \alpha^k \zeta^k, \tag{26}$$

where k is the number of iterations and the step α^k of the gradient method is selected so that functional (3) diminishes at each step.

Steps 1–4 are repeated until a desired calculation accuracy is achieved, for example, until the value of the functional becomes less than a preset value. A vector of parameters q^N obtained at the last step provides a solution to the problem.

Unlike Section 2.2, here there is no need for step 4, since the constraints are taken into account in the new extended functional.

3. NUMERICAL EXPERIMENTS IN HEAT CONDUCTION PROBLEMS

A simple example of the problem studied is analysis of temperature fields in a sample with the subsequent determination of the coefficients of related equations. Let us demonstrate the efficiency of our data processing method by finding the thermal conductivity (thermal diffusivity) of a sample from measured temperature values.

(1) Thermal conductivity of single crystals. To verify the method, we turn to the classical results of Ioffe and Ioffe for the thermal conductivity of single crystals [5]. As in [5], assume that experimental conditions are such that the conventional heat conduction equation

$$\frac{\partial T(\tau, x)}{\partial \tau} = \frac{k}{c}\frac{\partial^2 T}{\partial x^2} \tag{27}$$

(τ is time; x is spatial coordinate; and T, k, and c are the temperature, thermal conductivity, and specific heat of the sample) is valid.

Our goal is to find the thermal conductivity coefficient k that provides the least deviation of a solution to (27) from an experimental curve.

Ioffe and Ioffe experimented with a NaCl single crystal sandwiched in copper blocks with the same initial temperature. The lower block was immersed in a coolant or liquid air. One thermocouple measured the temperature difference $T_1 - T_2$ between the blocks; the other, the temperature T_2 of the upper block relative to room temperature T_0. The readings of both thermocouples were taken in 30-s intervals for the measurement time $\tau_m = 7$ min and tabulated (Table 1).

Table 1. Experimental data for the determination of the NaCl thermal conductivity [5]

Measurement no.	τ, s	$T_1 - T_2$	T_2
1	60	7.7	0.22
2	90	10.7	1.5
3	120	12.3	3.2
4	150	13.4	5.0
5	180	13.9	6.85
6	210	14.2	8.75
7	240	15.0	10.7
8	270	15.2	12.75
9	300	16.1	14.80
10	330	16.3	16.85
11	360	16.7	18.95
12	390	16.8	21.0
13	420	16.8	23.1

Table 2. Absolute temperature values

Measurement no.	τ, s	T_2	T_1
1	0	24	24
2	60	23.78	16.08
3	90	22.5	11.8
4	120	20.8	8.5
5	150	19	5.6
6	180	17.5	3.25
7	210	15.25	1.05
8	240	13.3	–1.7
9	270	11.25	–3.95
10	300	9.2	–6.9
11	330	7.15	–9.15
12	360	5.05	–11.65
13	390	3	–13.80
14	420	0.9	–15.9

When using Table 1 [5], it is necessary to make two assumptions. First, since in the experiment provision was made for preventing heat losses, we may consider the problem as one-dimensional and direct the x axis normally to the block–sample interfaces from the warm to cold block, i.e., from top to bottom. Second, since the temperature gradient in the experiment varies slowly, we may linearly interpolate in time the temperature values at the points $x = 0$ and L, where the measurements were taken. The point $x = 0$ lies at the warm block–sample interface; the point $x = L$ ($L = 0.64$ cm), at the sample–cold block interface.

The absolute temperature values are listed in Table 2 (the initial temperature was $T_0 = 24$°C).

We discretize Eq. (27) over space, introduce a uniform mesh $\{x_i = ih, h = L(K-1)\}$ (where $i = 0, \ldots, K-1$), take into consideration that the temperature distribution depends parametrically on the thermal conductivity, and obtain the set of differential–difference equations

$$\frac{\partial T(\tau, x_i, k)}{\partial \tau} = \frac{k}{c}(T(\tau, x_{i-1}, k) - 2T(\tau, x_i, k) + T(\tau, x_{i+1}, k)); \quad i = 1, \ldots, K-2 \tag{28}$$

with the initial condition

$$T(0, x_i, k) = T_0; \quad i = 0, \ldots, K-1 \tag{29}$$

and boundary conditions

$$T(\tau, x_0, k) = T_2(\tau); \quad \forall \tau \in [0, \tau_m]; \tag{30}$$

$$T(\tau, x_{K-1}, k) = T_1(\tau); \quad \forall \tau \in [0, \tau_m]. \tag{31}$$

The only unknown parameter in set (28) is the thermal conductivity k.

The final sum of squares of discrepancies between temperatures calculated (by model (27)) and measured at all time points,

$$F(k) = \sum_{i=1}^{K-2} (T(\tau_m, x_i, k) - \bar{T}(\tau_m, x_i))^2, \tag{32}$$

gives the quality functional for the problem of experimental data processing.

Unfortunately, the function $\bar{T}(\tau_m, x)$ [5] is known only at the points $x = 0$ and L. Since the boundary conditions are approximated linearly, we may assume that the second derivative on the left of (27) is constant and, hence, the function is quadratic in x. For the function $\bar{T}(\tau_m, x)$, we took a parabola $ax^2 + bx$, since only two coefficients can be found by two points.

Calculation was performed for 40 randomly selected initial approximations that were uniformly distributed over the closed interval [0.005, 0.025]. The outcome exceeded our expectations. The average calculated thermal conductivity was $k = 0.012$, rather than $k = 0.013$, which was previously obtained by Ioffe. At the end of the calculation, the integral deviation of the calculated data from the quality functional (measured data) was found to be 9×10^{-3}.

Figure 1 shows a typical curve of convergence in the problem of thermal conductivity of single crystals.

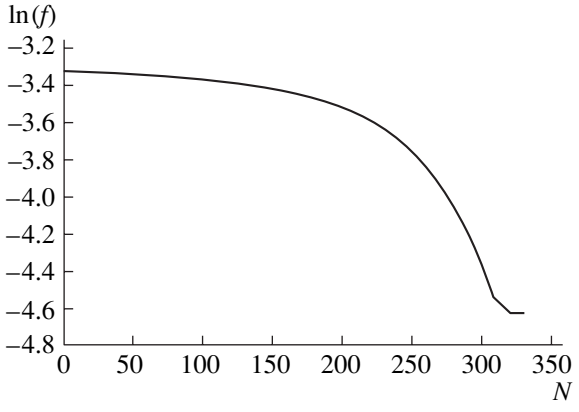

Fig. 1. Convergence for the quality functional f vs. number N of iterations upon calculating the thermal conductivity.

(2) Thermal diffusivity of a plate. By way of second example, let us consider the problem of thermal diffusivity [6] of a plate of thickness $h = 10$ cm. On one side of the plate, the temperature was T_0; on the other side and at the middle of the plate, the temperature oscillation amplitudes were $\Delta T_1 = 10$°C and $\Delta T_2 = 8$°C, respectively. The oscillation period on the other side was $\tau_0 = 1$ h.

In [6], the thermal diffusivity value was found by plotting the Fourier test and turned out to be $a = 0.009$ m^2/h.

Let us formalize the statement of the problem to apply our method. The temperature variation is described by the equation

$$\frac{\partial T(\tau, x)}{\partial \tau} = a\frac{\partial^2 T}{\partial x^2}, \quad (33)$$

where τ is time; x is the spatial coordinate; and T and a are the sample temperature and thermal diffusivity, respectively.

We discretize Eq. (33) over the coordinate x, introduce a uniform mesh $\{x_i = ir, r = h/(K-1)\}$ (where $i = 0, \ldots, K-1$), take into consideration that the temperature distribution depends parametrically on the thermal diffusivity, and obtain the set of differential–difference equations

$$\frac{\partial T(\tau, x_i, a)}{\partial \tau} = a(T(\tau, x_{i-1}, a) - 2T(\tau, x_i, a) + T(\tau, x_{i+1}, a)), \quad i = 1, \ldots, K-2 \quad (34)$$

with the initial condition

$$T(0, x_i, a) = T_0; \quad i = 0, \ldots, K-1 \quad (35)$$

and boundary conditions

$$T(\tau, x_0, a) = T_0 + \Delta T_1 \sin\left(2\pi\frac{\tau}{\tau_0}\right); \quad \forall \tau \in [0, \tau_m]; \quad (36)$$

$$T(\tau, x_{K-1}, a) = T_0; \quad \forall \tau \in [0, \tau_m]. \quad (37)$$

The only unknown parameter in set (34) is the thermal diffusivity a.

In order to write the quality functional, we must know the time dependence of the temperature in the middle of the sample, $\bar{T}(\tau, h/2)$. The period of temperature oscillation at this place is unknown, and we cannot take it to be equal to τ_0, since the thermal diffusivity would indefinitely increase in this case. Let the oscillation period at the middle be $\tau_{h/2} = 2\tau_0$ and let the measurement time be $\tau_m = \tau_0/2$. Bearing in mind that the plate is thin and the temperature conditions are quasi-steady-state [6], we linearly interpolate temperature values between the points $x = 0$, $h/2$, and h and designate the temperature distribution thus obtained as $\bar{T}(\tau_m, x)$. Then, the quality functional has the form

$$F(a) = \sum_{i=1}^{K-2} (T(\tau_m, x_i, a) - \bar{T}(\tau_m, x_i))^2. \quad (38)$$

The results are in good agreement with those obtained in [6]. Calculation was made for 20 randomly selected initial approximations that were uniformly distributed over the segment [0.0006, 0.0180]. The mean value of the thermal diffusivity was found to be $a = 0.0094$ versus $a = 0090$ in [6]. The final value of the quality functional was 23.63.

4. NUMERICAL EXPERIMENTS ON MOLECULAR BIOLOGY DATA PROCESSING

A comparatively new area of application of the algorithm suggested is the processing of huge data arrays, for example, simultaneous search for many hundreds of phenomenological parameters in mathematical problems of biology and genetics, in particular, in the gene chain model. Protein concentration greatly varies upon the evolution of a biological object and is measured with high accuracy, but finding a correlation of these data with any of the advanced theoretical models is a challenge. In one of them, the dynamics of a system is described by nonlinear diffusion reaction equations (NDREs), which contain 50 or more parameters on most of which inequality constraints are imposed.

The molecular biology problem of segment determination in a standard biological system, the fruit fly (*Drosophila melanogaster*) embryo, was stated in detail in [1]. The mathematical statement of the problem involves the set of NDREs

$$\frac{\partial v_i^a}{\partial t} = R^a g(w_i^a) + D^a[(v_{i+1}^a - v_i^a) + (v_{i-1}^a - v_i^a)] - \lambda^a v_i^a, \quad (39)$$

where the argument of g is

$$w_i^a = \sum_{j=0}^{N-1} T^{aj} v_i^j + m^a v_i^{\mathrm{bcd}} + h^a.$$

The basic element of the gene chain model is the matrix T, which characterizes a gene chain. Its elements T^{aj} describe the interplay between the concentration of one protein (the product of one gene) and the concentration of another protein (the product of another gene) by using a particular number specific for any pair of a and j.

The control actions of the protein that is the Bicoid product of maternal gene *bcd* are taken into account as an external perturbation (it is specified by the parameter m^a), and the parameter h^a reflects the threshold value of regulatory action.

Let the position of a nucleus on the longitudinal axis of the embryo be defined by index i and let all nuclei contain a copy of a regular chain of N genes, which is characterized by an $N \times N$ matrix T.

The first term on the right of (39) stands for gene regulation and protein synthesis, with the parameter R^a defining the level of synthesis. The second term describes gene product (protein) exchange between neighboring nuclei, with the parameter D^a standing for the exchange rate. The parameter λ^a describes the half-life period of the protein; the third term, gene product cleavage.

Differential constraints for the function f in (1) are given by a set of nonlinear equations like (39). Numerical simulation is aimed at determining $N(N + 5)$

Table 3. Results of calculations (see text)

Value of functional	2	3	4	5	6
<1	2(7229)	–	–	–	100(512621)
<10	13(48840)	3(77896)	–	3(449563)	–
<50	41(46000)	9(31755)	21(56027)	27(96432)	–
<100	50(52341)	9(31755)	39(54134)	33(123410)	–
>100	50(69730)	91(69873)	61(98863)	67(301301)	–

parameters of the system, where N is the number of genes.

Observables are patterns of gene activity, which supposedly are solutions to equations like (39). A desired set of parameters is that providing the closest fit of these solutions to experimental data. As before, it is necessary to minimize the sum of squares of discrepancies between the concentrations of all proteins that were calculated by the gene chain model and found in independent experiments. The sum is taken over all nuclei and all time instants for which experimental data are available.

(1) Test for efficiency of the method. Let us apply our method to data processing and finding the phenomenological parameters of a model described by a set of several hundreds of NDREs (like model (39)).

Consider a system that describes a regulatory chain of only two genes. In this case, we have 16 equations with $2(2 + 5) = 14$ parameters.

We take a certain set of parameters and solve the direct problem, i.e., integrate system (1). Let known values of the function $y(t_i) = (y_0(t_i), \ldots, y_{K-1}(t_i))^T$ be quantities $v(t_i, q) = (v_0(t_i, q), \ldots, y_{K-1}(t_i, q))^T$ that were calculated for a given number J of points over a given time interval ($i = 1, \ldots, J$) (so-called artificial data). Now, with these data, we will try to recover the initial set of parameters. In this case, the quality functional at the point of global maximum is known and equals zero.

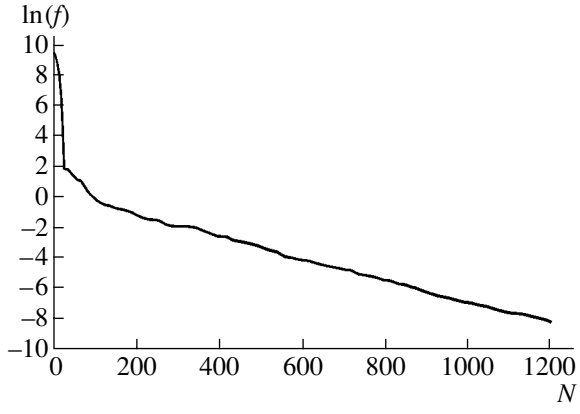

Fig. 2. The same as in Fig. 1 upon determining phenomenological parameters in the problem of molecular biology.

This allows us to estimate the quality of a solution from the value of the functional.

Let inequality constraints be imposed on six parameters linearly entering into set (39). We introduce an exponentially increasing penalty function that depends on a complex consisting of the remaining eight parameters and solve the problem of minimization numerically in the same way as before.

Calculation was performed for 100 randomly selected initial approximations that were uniformly distributed in the parameter space. For each of the initial points, we obtained several results by the method of simulated annealing [7] and the gradient method. In the latter, inequality constraints were transformed algebraically and trigonometrically (sin-transformation and tanh-transformation with various γ).

Calculation was terminated if the functional changed by less than a specified quantity at each step from a given number of steps. The set of parameters q obtained at the last step was taken to be optimal.

The numerical results listed in Table 3 are totally consistent with the theory. Columns 2–6 show the percentage of trials (initial points) when the functional falls into the interval indicated in column 1. The parenthesized figures mean the average number of integrations of the set of equations or, in other words, machine time costs. Column 6 shows the values obtained by the random search (simulated annealing) method; column 5, by the gradient method with algebraic transformation of constraints; and columns 3 and 4, by the gradient method with tanh- and sin-trigonometric transformations, respectively.

The optimal point and the number of steps turned out to be dependent on the initial approximation. For each of the initial points, calculations with tanh-transformations with various arbitrary coefficients γ were performed and the best result for each of the points was taken. These calculations are summarized in column 2.

The basic conclusions following from the calculation results are as follows.

The modified gradient method may be used to advantage in searching for the quality functional minimum when large data arrays are processed.

With the initial point selected appropriately, the number of steps needed for this method to become con-

vergent is two orders of magnitude smaller than in the random search method.

The most efficient transformation of inequality constraints is impossible to choose in advance; however, the proper selection of the parameter of tanh-transformation provided the highest rate of convergence (see Fig. 2).

DISCUSSION

Our numerical experiments show that the suggested method of processing large data arrays for finding the most appropriate parameters of a given mathematical model has a number of advantages. Namely, it offers a high rate of convergence and is applicable even if experimental data are not independent, for example, if the elements of the vector $y(t_i)$ ($i = 1, \ldots, J$) represent a Markovian sequence. In this case, the function $\varphi(v(t_1, q), \ldots, v(t_J, q))$ in (3) takes the form

$$\sum_{i=1}^{J} \ln\left[\frac{1}{\sigma_1(t_i)\sqrt{2\pi}}\exp\left\{-\frac{[y_1(t_i) - v_1(t_i, q)]^2}{2\sigma_1^2(t_i)}\right\}\right]$$

$$+ \ln\left[\frac{1}{\sigma_2(t_i)\sqrt{2\pi(1-\rho^2(t_i))}}\exp\left\{-\frac{1}{2\sigma_2^2(t_i)(1-\rho^2(t_i))}\right.\right.$$

$$\left.\left.\times\left[y_2(t_i) - v_2(t_i, q) - \frac{\rho(t_i)\sigma_2(t_i)}{\sigma_1(t_i)}(y_1(t_i) - v_1(t_i, q))\right]^2\right\}\right] \quad (40)$$

$$+ \ln\left[\frac{1}{\sigma_K(t_i)\sqrt{2\pi(1-\rho^2(t_i))}}\exp\left\{-\frac{1}{2\sigma_K^2(t_i)(1-\rho^2(t_i))}\right.\right.$$

$$\left.\left.\times\left[y_K(t_i) - v_K(t_i, q) - \frac{\rho(t_i)\sigma_K(t_i)}{\sigma_{K-1}(t_i)}\right.\right.\right.$$

$$\left.\left.\left.\times(y_{K-1}(t_i) - v_{K-1}(t_i, q))\right]^2\right\}\right].$$

In [7, 8], a version of the random search method (the method of simulated annealing or the Metropolis method) was applied to find phenomenological parameters that provide a global minimum of the quality functional in a similar problem of mathematical biology. It was shown that the given functional has many local minima but simulated annealing "bypasses" them, finding a global minimum.

However, the use of simulated annealing necessitates multiple integration of a set of strong nonlinear differential–difference diffusion reaction equations. Note for comparison that, in the case of the random search method, finding each subsequent approximation to the entire vector of parameters requires that the quality functional be calculated as many times as the number of the parameters involved, while in the gradient method, only once. This fact may become of special significance when a large number of proteins (the products of gene activity) is considered, since the number of integrations necessary for random search grows as the number of proteins squared.

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