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Sensitivity Analysis and Practical Identifiability of Some Mathematical Models in Biology

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Abstract—We study the identifiability of some mathematical models of spreading TB and HIV coinfections in a population and the dynamics of HIV-infection at the cellular level. Sensitivity analysis is carried out using the orthogonal method and the eigenvalue method which are based on studying the properties of the sensitivity matrix and show the effect of the model coefficient change on simulation results. Practical identifiability is investigated which determines the possibility of reconstructing coefficients from the noisy experimental data. The analysis is performed using the correlation matrix and Monte Carlo method, while taking into consideration the Gaussian noise in measurements. The results of numerical calculations are presented on whose basis we obtain the identifiable sets of parameters.

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INTRODUCTION

Systems of ordinary differential equations (ODEs) are a powerful tool for simulating dynamic processes in biology; e.g., immunology [1], epidemiology [2], pharmacokinetics [3-5], etc. The coefficients of ODE systems characterize the properties of the model. Finding the coefficients provides information about diseases, the immune status of a body, spreading of the epidemic, drug susceptibility, etc. These coefficients can be estimated (and sometimes uniquely determined) using various additional information about biological processes (solution of the Cauchy problem for ODEs) at fixed times. The problem of determining the model parameters based on additional information about the solution of the direct problem is called an *inverse problem* [6]. However, before solving the inverse problem it is necessary to find the correctness conditions (existence, uniqueness, and/or stability of the solution). Identifiability analysis allows us to find some correctness conditions for the inverse problem [7].

The history of development of identifiability of mathematical models goes back to the 80s of the twentieth century, when the basic concepts and definitions were introduced [8–10]. Important first results are presented in [11–13], where the identifiability conditions are obtained for nonlinear systems of differential equations. In [14–16], the identifiability conditions for linear systems are obtained, and, in [17], the problem of parametric identifiability is under study in the presence of disturbances in the measurements. In [18], a new approach is developed for studying the global structural identifiability of linear dynamic models, and, in [12, 19], some theorems related to the control of the system structure are proved. In [20, 21], the properties and practical aspects of identification in the fields of metabolism, pharmacokinetics, ecology, and chemical kinetics are considered. In [22, 23], verification of a priori

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global identifiability of some nonlinear models is carried out; and in [24, 25], a new separation algorithm for identifiability analysis is developed. In [3, 4], an integrated approach is proposed to an advanced methodology of mathematical models of physiology and medicine; in [5], a new approach to the analysis of a priori identifiability of isolated systems is suggested; and in [26], analysis of structural identifiability for the problems of cell biology is performed.

Analysis of identifiability can conventionally be divided into the three groups:

1. *Structural* (*a priori*) *identifiability* which analyzes the structure of the model and data and does not take into account the quantity and quality of additional measurements of the inverse problem (measurements are carried out under ideal conditions). Structural identifiability methods include the methods of subordinate functions, differential algebra, Taylor series expansion, etc. [27, 28].

2. *Sensitivity analysis* which determines the degree of influence of the parameters and initial conditions of the model on simulation results. The methods of sensitivity analysis require knowledge of the initial parameters of the model, with respect to which the sensitivity is investigated, as well as the location and number of measurements. Sensitivity methods include the eigenvalue method, the orthogonal and correlation methods, etc. [7, 29].

3. *Practical* (*a posteriori*) identifiability depends on the quantity and quality of experimental data (the error level in measurements is set). For the analysis of practical identifiability, Monte Carlo method, the correlation matrix method, DAISY, etc. are used [30].

In this article, the mathematical models of the tuberculosis and HIV coinfection spreading in a population (Section 3), and the dynamics of HIV infection at the cellular level (Section 4) are under study in terms of their identifiability; these models are investigated by sensitivity analysis methods (Section 1) and practical identifiability (Section 2). Some set of identifiable parameters is obtained for each model.

1. SENSITIVITY ANALYSIS

Sensitivity analysis is used for evaluating the identifiability of unknown parameters q of a model in the form of the ODE system

$$\begin{aligned} \dot{x}(t) = g(t, x(t), q), \qquad & t \in (0, T), \\ x(0) = x_0, & \\ h(t, x(t), q) = f(t), & \end{aligned} \tag{1}$$

where $x(t) \in C^1(\mathbb{R}^M)$ is a vector of functions (M is the number of equations), $q \in \mathbb{R}^L$ is a vector of parameters (L is the number of parameters), $f(t) \in C(\mathbb{R}^P)$ is a function of measurements ($P \leqslant M$ is the number of functions being measured), and t is time.

Sensitivity analysis methods do not require actual experimental data, although knowledge of the number of measurements and the times when these measurements were taken, may be necessary [29, 31]. To study a mathematical model using sensitivity analysis methods, we need to know the parameter values that may be available from the literary sources or statistical information.

Sensitivity analysis methods are based on studying the sensitivity matrix. Assume that

$$t_1 \leqslant t_2 \leqslant \cdots \leqslant t_K$$

are the times when the vector function $f(t)$ will be measured. Then the sensitivity matrix coefficients for a given parameter vector q^* are calculated by the formula

$$s_{ij}(t) = \frac{\partial f_i(t, q^*)}{\partial q_j},$$

where f_i is the ith component of the measurement vector f, $i = 1, \ldots, P$, and q_j is the jth component of the parameter vector, $j = 1, \ldots, L$.

Thus, the sensitivity matrix is defined as

$$S_{P\cdot K\times L}=\begin{pmatrix} s_{11}(t_1) & \dots & s_{1L}(t_1)\\ \vdots & \ddots & \vdots\\ s_{P1}(t_1) & \dots & s_{PL}(t_1)\\ \dots\dots\dots\dots\dots\dots\dots\\ s_{11}(t_K) & \dots & s_{1L}(t_K)\\ \vdots & \ddots & \vdots\\ s_{P1}(t_K) & \dots & s_{PL}(t_K)\end{pmatrix}. \tag{2}$$

To calculate the sensitivity matrix, we consider the traditional sensitivity function

$$s_{q_j}(t)=\frac{\partial x}{\partial q_j}(t),\qquad j=1,\dots,L.$$

By differentiating the first equation of system (1) with respect to q_j, we obtain that each vector function s_{q_j}, $j=1,\dots,L$, satisfies the Cauchy problem

$$\begin{gathered}\dot s_{q_j}(t)=\frac{\partial g}{\partial x}(t,x(t;q),q)s_{q_j}(t)+\frac{\partial g}{\partial q_j}(t,x(t;q),q),\\ s_{q_j}(t_0)=0.\end{gathered} \tag{3}$$

Solving (3), we obtain $s_{q_j}(t)$. Then, differentiating the third equation of (1) with respect to q_j, we find that the sensitivity matrix coefficients are calculated as

$$s_{ij}=\frac{\partial h_i}{\partial x}\,s_{q_j}+\frac{\partial h_i}{\partial q_j},\qquad i=1,\dots,P,\qquad j=1,\dots,L.$$

Next, we will consider the orthogonal method and the eigenvalue method of analysis of the properties of the sensitivity matrix S.

1.1. Orthogonal Method

The main idea of the orthogonal method proposed in [32] is to investigate the linear dependences of the columns of the sensitivity matrix S defined by (2). Thus, we can simultaneously evaluate both the sensitivity of the parameters to the input data and the relationship between the parameters. In the literature, there are several variants of determining the linearly dependent columns of a matrix, two of which we consider as the main approaches and describe as two algorithms; other variants are variations of the basics.

Algorithm 1 of the Orthogonal Method [33].

Step 1. We define a stopping criterion δ_1, an array $I=\varnothing$ of the numbers of the identifiable parameters, and an array $U=\{1,\dots,L\}$ of the numbers of nonidentifiable parameters $U=\{1,\dots,L\}$. We construct the sensitivity matrix S of the form (2).

Step 2. Select the column l with the largest sum of squares of elements, add l to the matrix E as the first column, and delete l from S. The element l is added to the array I and removed from U.

Step 3. If U is empty then we stop the algorithm: for this model, all parameters are identifiable. Otherwise, go to Step 4.

Step 4. For each column S_h, $h=1,\dots,n$, of the matrix S, where n is the number of remaining columns from S, we calculate the perpendiculars:

$$S_h^{\perp}=S_h-S_h^{\mathrm{proj}},\qquad S_h^{\mathrm{proj}}=\sum_{k=1}^{L-n}\frac{(S_h,E_k)}{(E_k,E_k)}\,E_k,\qquad E=(E_1,...,E_{L-n}),\qquad h=1,\dots,n.$$

Step 5. From the resulting matrix $S^{\perp}$ of perpendiculars, we select a column l with the largest sum of squares of elements. If $\|S_l^{\perp}\| \leqslant \delta_1$ then we halt the algorithm. All parameters from I are identifiable; otherwise, go to Step 6.

Step 6. Add the element l to I, delete it from U, add the corresponding column to E and remove it from S. Proceed to Step 3.

In [32], the process of selecting identifiable parameters is halted as soon as the maximum value is below the cutoff value $\delta_1 \approx 0$, the choice of which is rather arbitrary. For instance, in [34] it is $\delta_1 = 10^{-4}$. In the present study, we do not apply a stopping criteria, but evaluate all parameters from the most identifiable to the least identifiable ones, and analyze the value of δ_1 in general.

Algorithm 2 of the Orthogonal Method [32].

Step 1. For each column of the sensitivity matrix S, we calculate the sum of squares of the entries.

Step 2. As the first parameter to be evaluated, we select the parameter corresponding to the column of the matrix S with the largest sum of squares of the entries.

Step 3. A column with the largest sum of squares of the entries is denoted by X_L ($L = 1$ for the first iteration).

Step 4. Calculate $\widehat{S}_L = X_L\left(X_L^{\top}X_L\right)^{-1}X_L^{\top}S$.

Step 5. Calculate the residual matrix R_L: $R_L = S - \widehat{S}_L$.

Step 6. For each column of the residual matrix R_L, calculate the sum of squares of the entries. The column with the largest sum corresponds to the next estimated parameter.

Step 7. Select the corresponding column in S and enlarge the matrix X_L by adding a new column. Denote the enlarged matrix by X_{L+1}.

Step 8. Set $L = L + 1$ and repeat Steps 4–7 until the column with the largest value of the sum of squares of the entries in the residual matrix becomes less than the specified cutoff value.

1.2. Method of Eigenvalues

The method of eigenvalues, proposed in [11], bases on the properties of the eigenvalues and eigenvectors of the matrix:

$$H_{ml} = \sum_{i,k} \frac{\partial f_i(t_k, q^*)}{\partial q_l} \frac{\partial f_i(t_k, q^*)}{\partial q_m} = (S^T S)_{ml}, \tag{4}$$

where S is the sensitivity matrix defined by (2) and q^* is a given vector of parameters.

Algorithm of the Method of Eigenvalues

Step 1. We set a stopping criterion δ_2, an array of identifiable parameters $I = 1, \ldots, L$, and an array of non-identifiable parameters $U = \varnothing$. Then we construct the sensitivity matrix S of the form (2).

Step 2. If I is empty then we halt the algorithm. For this model, all parameters are non-identifiable. Otherwise, go to Step 3.

Step 3. We calculate the matrix H by formula (4). For H we find the eigenvalues λ^l:

$$\lambda^1 \leqslant \lambda^l \leqslant \cdots \leqslant \lambda^L$$

and eigenvectors u^l.

Step 4. If $\lambda^1 \geq \delta_2$ then we halt the algorithm. The parameters that are in I are identifiable. Otherwise, go to Step 5.

Step 5. Choose l: $\left|u_l^1\right| = \max\left(\left|u_1^1\right|, \left|u_2^1\right|, \ldots, \left|u_L^1\right|\right)$ (the maximal element in the eigenvector with the minimal eigenvalue). Add l to the set of nonidentifiable parameters U, delete from I, delete the corresponding column from the matrix S, and go to Step 2.

As in the previous method, we evaluate all parameters without selecting a cutoff value for $\delta_2 \approx 0$, from the most identifiable to the least identifiable ones.

2. PRACTICAL IDENTIFIABILITY

Analysis of practical identifiability allows us to evaluate the model parameters with acceptable accuracy on the basis of some noisy experimental data. The result of application of the practical identifiability methods for the analysis of mathematical models depends on the quality and quantity of experimental data. Suppose that the measurements are given with some error

$$f(t) = h(t, x(t), q) + \varepsilon(t), \tag{5}$$

where $\varepsilon(t)$ is a normally distributed error with zero mean and variance $\sigma^2(t)$.

Next, we consider methods of practical identifiability: the Monte Carlo method and the correlation matrix method.

2.1. Correlation Matrix Method

In [35], an approach is proposed to study the correlations between the model parameters. The method calculates a matrix whose elements show a correlation between the two parameters. If this correlation is close to 1 then these two parameters depend on each other and are indistinguishable in the model; i.e., they cannot be evaluated separately.

Algorithm of the Correlation Matrix Method

Step 1. Set the exact values of the parameters q^0 that may be available from statistical information or the literature.

Step 2. Construct the sensitivity matrix S by formula (2).

Step 3. Let us construct the Fisher matrix by the formula

$$F = \sum_{k=1}^{K} \left(\frac{\partial f(t_k, q^0)}{\partial q} \right)^{\top} V^{-1} \left(\frac{\partial f(t_k, q^0)}{\partial q} \right) = S^{\top} V^{-1} S,$$

where K is the number of measurements, V is a known positive definite matrix of weights.

Step 4. Calculate the matrix $C = F^{-1}$.

Step 5. Calculate the correlation coefficients R_{ij} by the formula

$$R_{ij} = \begin{cases} c_{ij}/\sqrt{c_{ii}c_{jj}}, & i \neq j, \\ 1, & i = j, \end{cases}$$

where c_{ij} are the entries of C.

Step 6. Construct the correlation matrix

$$R = \begin{pmatrix} R_{11}(q_1, q_1) & \dots & R_{1L}(q_1, q_L) \\ \vdots & \ddots & \vdots \\ R_{L1}(q_L, q_1) & \dots & R_{LL}(q_L, q_L) \end{pmatrix}.$$

The correlation matrix method allows us to check the distinguishability of every pair of parameters. We should also note that the method identifies an indistinguishable pair and does not indicate the parameter that is more unidentifiable.

2.2. Monte Carlo Method

The Monte Carlo method [36] is a sampling method that uses random numbers and probability distributions. The method allows us to simulate various scenarios with different number of observations at different noise levels or measurement errors for different experimental designs when such projects may turn out to be impossible for practical experiments.

Algorithm of the Monte Carlo Method

Step 1. Set the exact values of the parameters q^0 which may be available from statistical information or the literature.

Step 2. Solve the direct problem

$$\dot{x}(t) = g(t, x(t), q), \qquad t \in (0, T),$$
$$x(0) = x_0,$$

and obtain the measurements $f(t_k)$ of the form (5) at fixed times t_k.

Step 3. Generate N sets (for example, $N = 100$) of the measurement data f with some given noise level ε.

Step 4. Solve the inverse problem for each of the N simulated datasets to find the parameter vector q^i, $i = 1, \ldots, N$.

Step 5. Calculate the average relative error of estimation (ARE) for each element of the vector q by the formula

$$\mathrm{ARE}_l = \frac{1}{N}\sum_{i=1}^{N}\frac{|q_l^0 - q_l^i|}{|q_l^0|}\cdot 100\,\%, \qquad l = 1, \ldots, L, \tag{6}$$

where q_l^0 is the lth parameter of vector q^0, while q_l^i, of q^i.

For a rather small measurement error, the parameters should be close to the true values and ARE should be close to zero. When the measurement error increases, the ARE value will also increase. If the ARE value is unacceptably high for some parameter, it can be argued that this parameter is not identifiable. Moreover, there is no clear rule on how high the ARE value should be before declaring a parameter unidentifiable for a specific problem.

We apply the above methods of analysis of sensitivity and practical identifiability to the mathematical models arising in epidemiology and immunology.

3. MATHEMATICAL MODEL OF SPREADING THE COINFECTION OF TUBERCULOSIS AND HIV

Consider the mathematical model of spreading the coinfection of tuberculosis (TB) and HIV developed by a group of American researchers [2]:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta c S\frac{I + J_3}{N} - \lambda\sigma S\frac{J^*}{R} - \mu S,\\
\frac{dL}{dt} &= \beta c(S + T)\frac{I + J_3}{N} - \lambda\sigma L\frac{J^*}{R} - (\mu + k + r_1)L,\\
\frac{dI}{dt} &= kL - (\mu + d + r_2)I,\\
\frac{dT}{dt} &= r_1 L + r_2 I - \beta c T\frac{I + J_3}{N} - \lambda\sigma T\frac{J^*}{R} - \mu T,\\
\frac{dJ_1}{dt} &= -\beta c J_1\frac{I + J_3}{N} + \lambda\sigma(S + T)\frac{J^*}{R} - (\alpha_1 + \mu)J_1,\\
\frac{dJ_2}{dt} &= \beta c J_1\frac{I + J_3}{N} + \lambda\sigma L\frac{J^*}{R} - (\alpha_2 + \mu + k^*)J_2 + r^* J_3, \qquad t \in (0, T),\\
\frac{dJ_3}{dt} &= k^* J_2 - (\alpha_3 + \mu + d^* + r^*)J_3,\\
\frac{dA}{dt} &= \alpha_1 J_1 + \alpha_2 J_2 + \alpha_3 J_3 - (\mu + f)A,
\end{aligned} \tag{7}$$

$$S(0)=S_0,\qquad L(0)=L_0,\qquad I(0)=I_0,\qquad T(0)=T_0,$$
$$J_1(0)=J_{1_0},\qquad J_2(0)=J_{2_0},\qquad J_3(0)=J_{3_0},\qquad A(0)=A_0.$$

Here

$S(t)$ is the number of uninfected individuals,

$L(t)$ is the number of individuals latently infected with TB (without HIV),

$I(t)$ is the number of individuals with active TB (without HIV),

$T(t)$ is the number of individuals cured of TB (without HIV),

$J_1(t)$ is the number of individuals infected with HIV (without TB),

$J_2(t)$ is the number of individuals infected with HIV and latently infected with TB,

$J_3(t)$ is the number of individuals infected with HIV and active TB,

$A(t)$ is the number of individuals with AIDS;

$N=S+L+I+T+J_1+J_2+J_3+A$ is the entire population,

$R=S+L+T+J_1+J_2$ is the "active" population,

$J^*=J_1+J_2+J_3$ are the persons infected with HIV.

The values of the parameters

$$\Lambda,\ \beta c,\ \lambda\sigma,\ \mu,\ k,\ k^*,\ d,\ d^*,\ f,\ r_1,\ r_2,\ r^*,\ \alpha_1,\ \alpha_2,\ \alpha_3,\ N$$

are represented in Table 1. The following vector is selected as the initial data:

$$S(0)=430,\qquad L(0)=3854.5,\qquad I(0)=16.875,\qquad T(0)=3.412,$$
$$J_1(0)=3.2757,\qquad J_2(0)=27.7,\qquad J_3(0)=1.4,\qquad A(0)=0.357.$$

Suppose that additional information about the three functions of the system (7) is set

$$I(t_k;q)=I^k(q),\qquad J_3(t_k;q)=J_3^k(q),\qquad A(t_k;q)=A^k(q),\qquad k=1,\dots,K. \tag{8}$$

Consider the uniform grid on the segment $(0,T)$, $T=5$ years, with a partition of $N=5000$ points; $K=5$ measurements are performed once a year.

We will analyze the sensitivity of all 16 parameters of mathematical model (7)

$$\Lambda,\ \beta c,\ \lambda\sigma,\ \mu,\ k,\ k^*,\ d,\ d^*,\ f,\ r_1,\ r_2,\ r^*,\ \alpha_1,\ \alpha_2,\ \alpha_3,\ N$$

using the orthogonal method and the eigenvalue method (the results are presented in Table 2 and Fig. 1).

Table 2 presents the collections of parameters sensitive to measurement errors arranged in the order of increasing sensitivity, which were obtained using the sensitivity analysis methods. Note that a slight mismatch between the sequences of sensitive parameters obtained by different methods of sensitivity analysis, is connected with rather close values of the estimating norms of the perpendiculars of the sensitivity matrix and of the smallest eigenvalues of the matrix H of (4) (see Fig. 1). In Fig. 1 we denote: A_1 is the collection of all 16 parameters of the system,

$$A_2=A_1\setminus\{\Lambda\},\qquad A_3=A_2\setminus\{N\},\qquad A_4=A_3\setminus\{r^*\},\qquad A_5=A_4\setminus\{\beta c\},$$
$$A_6=A_5\setminus\{\alpha_1\},\qquad A_7=A_6\setminus\{\lambda\sigma\},\qquad A_8=A_7\setminus\{f\},\qquad A_9=A_8\setminus\{\mu\},$$
$$A_{10}=A_9\setminus\{k\},\qquad A_{11}=A_{10}\setminus\{k^*\},\qquad A_{12}=A_{11}\setminus\{d\},\qquad A_{13}=A_{12}\setminus\{d^*\},$$
$$A_{14}=A_{13}\setminus\{r_1\},\qquad A_{15}=A_{14}\setminus\{r_2\},\qquad A_{16}=A_{15}\setminus\{\lambda_2\}.$$

However, most of the parameters of mathematical model (7) can be determined quite accurately from statistical information and do not need to be clarified. Therefore, it is expedient to carry out the further analysis of identifiability for the shorter vector of parameters

$$q=(k,k^*,r_2,\alpha_1,\alpha_2,\alpha_3)\in\mathbb{R}^6.$$

Table 1. Parameters for mathematical model (7)

Parameters	Values	Units of measurement	Description
Λ	43	1/year	Birth rate
βc	0.025	—	Probability of contracting tuberculosis through contact with a person with active tuberculosis
$\lambda\sigma$	0.0004	—	Probability of contracting HIV through contact with an HIV-infected person
μ	0.0143	1/year	Natural mortality per capita
k	0.05	year	TB progression rate per capita for people not infected with HIV
k^*	0.25	year	TB progression rate per capita for people also infected with HIV
d	0.1	1/year	Tuberculosis mortality per capita
d^*	0.2	1/year	HIV mortality rate per capita
f	0.5	1/year	AIDS mortality rate per capita
r_1	3	1/year	Recovery indicator for latent tuberculosis per capita for people without HIV
r_2	1	1/year	Recovery indicator for active tuberculosis per capita for people without HIV
r^*	3	1/year	Recovery indicator for latent tuberculosis per capita for people with HIV
α_1	0.1	year	Per capita AIDS progression rate for individuals from J_1
α_2	0.2	year	Per capita AIDS progression rate for individuals from J_2
α_3	0.2	year	Per capita AIDS progression rate for individuals from J_3
N	4315.76	Number of individuals	The entire population

Table 2. Collections of all coefficients of model (7) that are sensitive to measurement errors (8)

Orthogonal method	Eigenvalue method
k, μ, α_2, d, r_2, r_1, f, $\lambda\sigma$,	α_3, α_2, r_2, r_1, d^*, d, k^*, k,
α_1, k^*, α_3, d^*, βc, r^*, Λ, N	μ, f, $\lambda\sigma$, α_1, βc, r^*, N, Λ

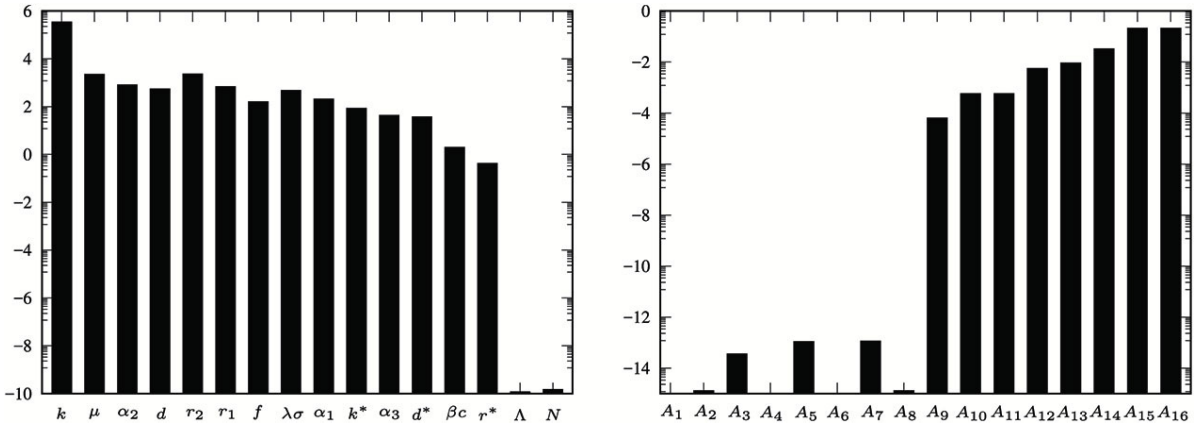

Fig. 1. The values of the norms of perpendiculars in a logarithmic scale for the orthogonal method (left) and the values of the minimal eigenvalues of matrix (4) in a logarithmic scale for the eigenvalue method (right) in the case of mathematical model (7).

Using the sensitivity analysis methods, we also obtained the collections of parameters that are sensitive to measurement errors. We arranged them in the order of increasing sensitivity that was obtained by sensitivity analysis (see Table 3).

The threshold values of the sensitive parameters δ_1 and δ_2 are set as follows: $\delta_1 = 10^{-3}$ for the orthogonal method, and $\delta_2 = 10^{-3}$ for the eigenvalue method.

Let us note the qualitative coincidence of the sequences of the sought parameters for various algorithms and methods. Fig. 2 presents the graphical illustration of the results:

The left and central graphs show the values of the norms of perpendiculars of the sensitivity matrix for the orthogonal method (Algorithms 1 and 2). Each column of these graphs represents the largest norm of a column of the matrix of perpendiculars to the sensitivity matrix, obtained at each iteration of the algorithm. The parameter corresponding to the column with the largest norm of perpendiculars is the least sensitive to measurement errors.

The right graph in Fig. 2 shows the values of the minimum eigenvalues of matrix (4) in the case of the eigenvalue method. At each iteration of the algorithm, based on the analysis of the minimal eigenvalue of matrix (4), the most sensitive parameter is determined. At the next iteration, the most sensitive parameter is excluded from consideration, and matrix (4) is rearranged for a new set of parameters. Under each column of the right graph in Fig. 2 a collection of parameters is presented which is considered at each iteration of the algorithm:

$$D_1 = \{\alpha_3, \alpha_1, k^*, \alpha_2, r_2, k\}, \qquad D_2 = \{\alpha_1, k^*, \alpha_2, r_2, k\},$$
$$D_3 = \{k^*, \alpha_2, r_2, k\}, \qquad D_4 = \{\alpha_2, r_2, k\}, \qquad D_5 = \{r_2, k\}.$$

For the correlation matrix method, we assume that $\sigma^2 = 1/60$ and measurements are taken with an error of 5 %. Then for $K = 2$ (the measurements are taken the first two years) we observe the correlation matrix of the form (9) and for $K = 5$ (measurements are taken every year), of the form (10):

Table 3. Collections of coefficients of the model (7) that are sensitive to measurement errors (8)

Orthogonal method		Eigenvalue method
Algorithm 1	Algorithm 2	
$k, \alpha_2, r_2, k^*, \alpha_1, \alpha_3$	$k, \alpha_2, r_2, k^*, \alpha_1, \alpha_3$	$k, r_2, \alpha_2, k^*, \alpha_1, \alpha_3$

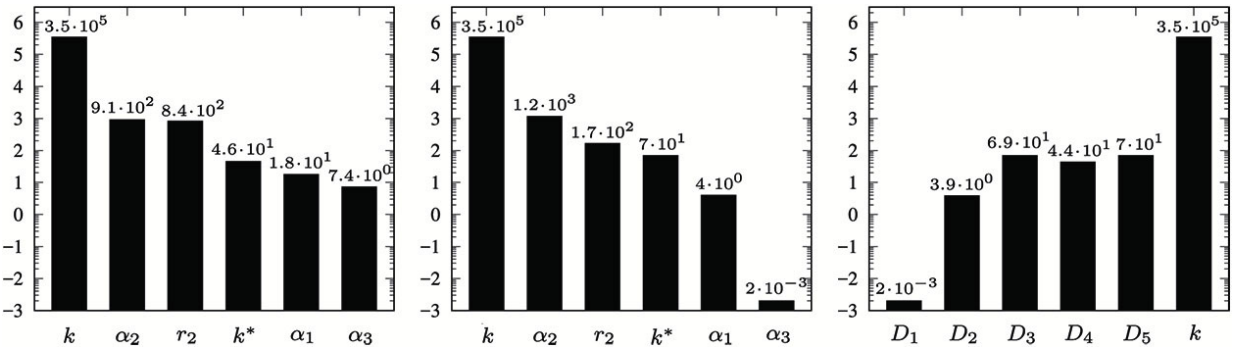

Fig. 2. The values of norms of perpendiculars in the logarithmic scale for the orthogonal method in the case of Algorithm 1 (left), in the case of Algorithm 2 (at the center), and the values of the minimal eigenvalues of matrix (4) in the logarithmic scale for the eigenvalue method (right) in the case of mathematical model (7).

$$R^2 = \begin{array}{c} \\ k \\ k^* \\ r_2 \\ \alpha_1 \\ \alpha_2 \\ \alpha_3 \end{array} \begin{array}{c} \begin{array}{cccccc} k & k^* & r_2 & \alpha_1 & \alpha_2 & \alpha_3 \end{array} \\ \begin{pmatrix} 1 & -6.7\times10^{-5} & 0.945 & 6.4\cdot10^{-5} & 6.7\cdot10^{-5} & -7.1\cdot10^{-5} \\ -6.7\cdot10^{-5} & 1 & 2.6\cdot10^{-5} & -0.835 & -0.975 & 0.998 \\ 0.945 & 2.6\cdot10^{-5} & 1 & -2.2\cdot10^{-5} & -1.7\cdot10^{-5} & 1.9\cdot10^{-5} \\ 6.4\cdot10^{-5} & -0.835 & -2.2\cdot10^{-5} & 1 & 0.696 & -0.814 \\ 6.7\cdot10^{-5} & -0.975 & -1.7\cdot10^{-5} & 0.696 & 1 & -0.984 \\ -7.1\cdot10^{-5} & 0.998 & 1.9\cdot10^{-5} & -0.814 & -0.984 & 1 \end{pmatrix} \end{array}, \quad (9)$$

$$R^5 = \begin{array}{c} \\ k \\ k^* \\ r_2 \\ \alpha_1 \\ \alpha_2 \\ \alpha_3 \end{array} \begin{array}{c} \begin{array}{cccccc} k & k^* & r_2 & \alpha_1 & \alpha_2 & \alpha_3 \end{array} \\ \begin{pmatrix} 1 & -4.2\cdot10^{-5} & 0.920 & 4.9\cdot10^{-5} & 5.1\cdot10^{-5} & -5.3\cdot10^{-5} \\ -4.2\cdot10^{-5} & 1 & 1.9\cdot10^{-5} & -0,752 & -0.994 & 0.997 \\ 0.920 & 1.9\cdot10^{-5} & 1 & 4.4\cdot10^{-6} & -3.1\cdot10^{-6} & 1.6\cdot10^{-6} \\ 4.9\cdot10^{-5} & -0.752 & 4.4\cdot10^{-6} & 1 & 0.696 & -0.739 \\ 5.1\cdot10^{-5} & -0.994 & -3.1\cdot10^{-6} & 0.696 & 1 & -0.998 \\ -5.3\cdot10^{-5} & 0.997 & 1.6\cdot10^{-6} & -0.739 & -0.998 & 1 \end{pmatrix} \end{array}. \quad (10)$$

Note that the correlation coefficients for the parameters (k, r_2) equal

$$R^2_{13}(k, r_2) = 0.945, \qquad R^5_{13}(k, r_2) = 0.920,$$

while for (k^*, α_3) we have

$$R^2_{26}(k^*, \alpha_3) = 0.998, \qquad R^5_{26}(k^*, \alpha_3) = 0.997$$

that are close to 1. It means that these parameters depend on each other and are indistinguishable for model (7). All other coefficients have rather low correlation. Consequently, to further determine the parameters of this model, it is desirable to fix the most sensitive parameters from the pairs (k, r_2) and (k^*, α_3). As shown by the sensitivity methods, the parameter r_2 is more sensitive to measurement errors than k, whereas α_3 is more sensitive than k^*. Therefore, it is recommended to fix the parameters r_2 and α_3 and determine the remaining four parameters.

Table 4. Collections of all coefficients of model (11) obtained by the methods of sensitivity analysis

Orthogonal method	Eigenvalue method
$N_T, \lambda_1, c, k_1, d_1, \delta, \rho_1, k_2, \lambda_2, \rho_2,$	$\lambda_1, d_1, m_1, \delta, k_2, \lambda_2, k_1, K_d, \lambda_E, \rho_2,$
$\delta_E, b_E, d_E, \lambda_E, m_1, d_2, K_b, K_d, m_2$	$\rho_1,\ d_2, c, d_E, N_T, K_b, m_2, b_E, \delta_E$

4. MATHEMATICAL MODEL OF THE DYNAMICS OF HIV INFECTION

Consider a mathematical model of the dynamics of HIV infection at the cellular level, which was developed by a group of American researchers (see [1]):

$$\begin{gathered}
\frac{dT_1}{dt} = \lambda_1 - d_1T_1 - k_1VT_1,\\
\frac{dT_2}{dt} = \lambda_2 - d_2T_2 - k_2VT_2,\\
\frac{dT_1^*}{dt} = k_1VT_1 - \delta T_1^* - m_1ET_1^*,\\
\frac{dT_2^*}{dt} = k_2VT_2 - \delta T_2^* - m_2ET_2^*, \qquad t \in (0,T),\\
\frac{dV}{dt} = N_T\delta\left(T_1^* + T_2^*\right) - cV - [\rho_1k_1T_1 + \rho_2k_2T_2]V,\\
\frac{dE}{dt} = \lambda_E + \frac{b_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b}\,E - \frac{d_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d}\,E - \delta_EE,\\
T_1(0) = T_{1_0}, \qquad T_2(0) = T_{2_0}, \qquad T_1^*(0) = T_{1_0}^*,\\
T_2^*(0) = T_{2_0}^*, \qquad V(0) = V_0, \qquad E(0) = E_0.
\end{gathered} \tag{11}$$

Here $t > 0$, $T_1^*(t)$ and $T_1(t)$ are concentration of the infected and uninfected CD4 + T lymphocytes, $T_2^*(t)$ and $T_2(t)$ are concentration of the infected and uninfected macrophages, respectively, $V(t)$ is the concentration of free viruses, and $E(t)$ is the concentration of CD8 + T-lymphocytes of effectors. The values of system parameters and initial data for mathematical model (11) are given in [38].

Suppose that the following additional information is available about system (11):

$$\begin{gathered}
T_1(t_k;q) + T_1^*(t_k;q) = T_1^k(q) + T_1^{*k}(q),\\
V(t_k;q) = V^k(q), \qquad E(t_k;q) = E^k(q), \qquad k = 1,\dots,K.
\end{gathered} \tag{12}$$

Consider the uniform grid on the segment $(0,T)$, $T = 100$ days, with a partition by $N = 10^4$ points; and assume that $K = 15$ measurements are taken uniformly.

Let us analyze the sensitivity of all 19 parameters

$$\lambda_1,\ \lambda_2,\ d_1,\ d_2,\ k_1,\ k_2,\ \delta,\ m_1,\ m_2,\ N_T,\ c,\ \rho_1,\ \rho_2,\ \lambda_E,\ b_E,\ d_E,\ K_b,\ K_d,\ \delta_E$$

of mathematical model (11). The results of analysis of the sensitivity of parameters arranged in the order of increasing sensitivity to measurements (12) are presented in Table 4 and Fig. 3.

For model (11), the results vary in dependence on the method. This is connected with the fact that most of the values of the estimating norms of perpendiculars of the sensitivity matrix and minimal eigenvalues are of the same scale (see Fig. 3), which implies the equality of occurrence of parameters in the sequence (a similar degree of sensitivity to the measurement errors).

In Fig. 3: A_1 is a collection of all 19 parameters, whereas

$$A_2 = A_1 \setminus \{\delta_E\}, \qquad A_3 = A_2 \setminus \{b_E\}, \qquad A_4 = A_3 \setminus \{m_2\}, \qquad A_5 = A_4 \setminus \{K_b\},$$

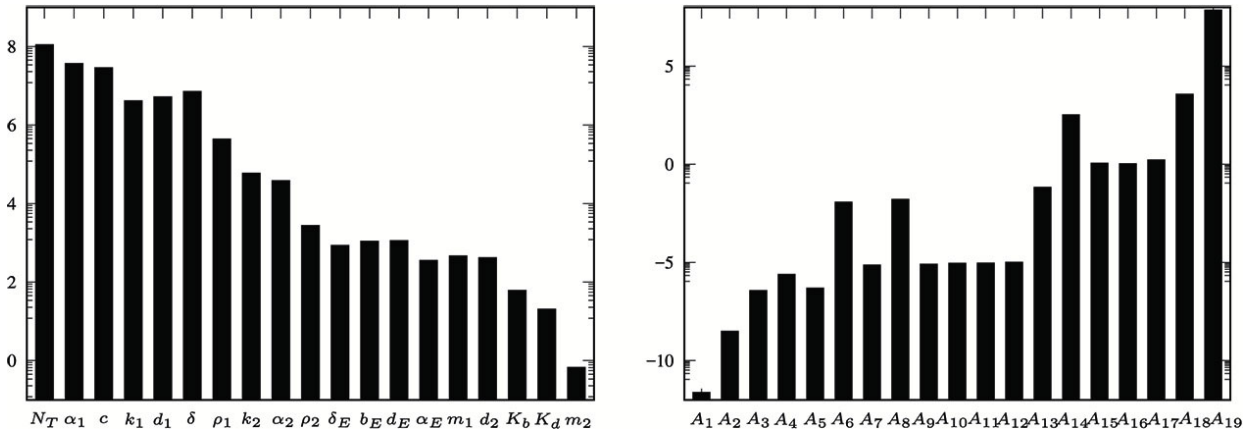

Fig. 3. The values of norms of perpendiculars in the logarithmic scale for the orthogonal method (left) and the values of the minimal eigenvalues of matrix (4) in the logarithmic scale for the eigenvalue method (right) in the case of mathematical model (11).

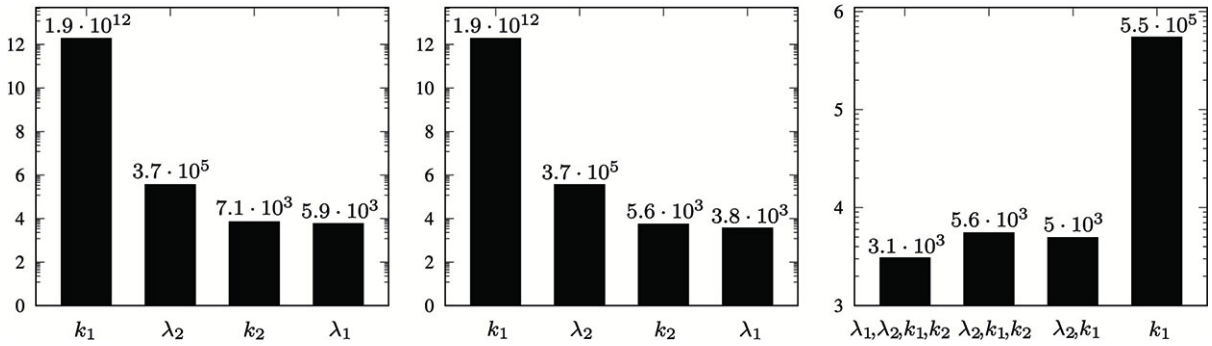

Fig. 4. The values of norms of perpendiculars in the logarithmic scale for the orthogonal method in the case of Algorithm 1 (left), in the case of Algorithm 2 (at the center), and the values of the minimal eigenvalues of matrix (4) in the logarithmic scale for the eigenvalue method (right) in the case of mathematical model (11).

$$A_6 = A_5 \setminus \{N_T\}, \qquad A_7 = A_6 \setminus \{d_E\}, \qquad A_8 = A_7 \setminus \{c\}, \qquad A_9 = A_8 \setminus \{d_2\},$$

$$A_{10} = A_9 \setminus \{\rho_1\}, \qquad A_{11} = A_{10} \setminus \{\rho_2\}, \qquad A_{12} = A_{11} \setminus \{\lambda_E\}, \qquad A_{13} = A_{12} \setminus \{K_d\},$$

$$A_{14} = A_{13} \setminus \{k_1\}, \qquad A_{15} = A_{14} \setminus \{\lambda_2\}, \qquad A_{16} = A_{15} \setminus \{k_2\},$$

$$A_{17} = A_{16} \setminus \{\delta\}, \qquad A_{18} = A_{17} \setminus \{m_1\}, \qquad A_{19} = A_{18} \setminus \{d_1\}.$$

Most parameters of mathematical model (11) can be found fairly accurately from the medical data and do not need to be clarified, and only four of them, namely λ_1, λ_2, k_1, and k_2, must be determined for each patient individually [39]. Therefore, further identifiability analysis is carried out for the significant parameter vector

$$q = (\lambda_1, \lambda_2, k_1, k_2) \in \mathbb{R}^4.$$

Applying the sensitivity analysis methods, we obtain the identical sets of parameters sensitive to the measurement errors and arrange them in the order of increasing sensitivity, which are presented in Fig. 4.

Note that all parameters of q are not very sensitive to the measurement errors (12) since $\delta_1 = \delta_2 = 10^3$. Thus, the solution q of the inverse problem (11), (12) will be stable to the data errors.

For the correlation matrix method we put $\sigma^2 = 1/30$, and assume that the measurements are given with error of 10 %. In this case, the correlation matrices are as follows:

Table 5. The values of the relative error of the form (6) obtained by Monte Carlo method for mathematical model (11)

Number of measurements	Noise level	Relative error			
		λ_1	λ_2	k_1	k_2
$K = 8$	5 %	8.54	44.12	10.18	47.61
	10 %	4.41	45.94	12.82	47.61
	15 %	15.65	45.96	7.66	49.01
$K = 15$	5 %	2.69	41.72	6.44	48.94
	10 %	3.54	44.79	4.32	48.14
	15 %	9.62	42.76	13.11	48.64

for $K = 4$:

$$R_4 = \begin{array}{c} \\ \lambda_1 \\ \lambda_2 \\ k_1 \\ k_2 \end{array} \begin{array}{c} \begin{array}{cccc} \lambda_1 & \lambda_2 & k_1 & k_2 \end{array} \\ \begin{pmatrix} 1 & 0.194 & 4.4 \cdot 10^{-3} & -0.648 \\ 0.194 & 1 & -0.859 & -0.753 \\ 4.4 \cdot 10^{-3} & -0.859 & 1 & 0.415 \\ -0.648 & -0.753 & 0.415 & 1 \end{pmatrix} \end{array}; \tag{13}$$

for $K = 8$:

$$R_8 = \begin{array}{c} \\ \lambda_1 \\ \lambda_2 \\ k_1 \\ k_2 \end{array} \begin{array}{c} \begin{array}{cccc} \lambda_1 & \lambda_2 & k_1 & k_2 \end{array} \\ \begin{pmatrix} 1 & 0.447 & -0.671 & -0.526 \\ 0.447 & 1 & -0.473 & -0.796 \\ -0.671 & -0.473 & 1 & 0.227 \\ -0.526 & -0.796 & 0.227 & 1 \end{pmatrix} \end{array}; \tag{14}$$

for $K = 15$:

$$R_{15} = \begin{array}{c} \\ \lambda_1 \\ \lambda_2 \\ k_1 \\ k_2 \end{array} \begin{array}{c} \begin{array}{cccc} \lambda_1 & \lambda_2 & k_1 & k_2 \end{array} \\ \begin{pmatrix} 1 & -0.267 & -0.495 & 0.358 \\ -0.267 & 1 & -0.368 & 0.154 \\ -0.495 & -0.368 & 1 & -0.710 \\ 0.358 & 0.154 & -0.710 & 1 \end{pmatrix} \end{array}. \tag{15}$$

Note that, in the cases of $K = 4$, $K = 8$, and $K = 15$, the correlation coefficients between the parameters are rather small. It means that the parameters are independent of each other and can be evaluated individually.

The results of applying the Monte Carlo method are given in Table 5 for different numbers of measurements and noise levels.

To solve the inverse problem (item 4 of the Monte Carlo method algorithm) for the mathematical model (11), a genetic algorithm was used [38]. At each iteration, the direct problem of the genetic algorithm was solved using the Runge–Kutta method of the fourth approximation order.

Monte Carlo method showed that the most unidentifiable parameters are k_2 and λ_2 since the values of the relative errors ARE obtained by (6), are sufficiently high. In [40], some confidence intervals for the considered parameters are constructed. It is shown that the confidence interval size for λ_1 is the smallest and equal to 0.002827, the confidence interval for λ_2 is the largest and equal to 0.244993; it is 0.024657 for k_1, and 0.084515 for k_2. The smaller the confidence interval for the parameters, the better it can be reconstructed.

Consequently [1], the parameter λ_1 is restored with the minimum relative error, whereas the λ_2 is determined worse than the others. These calculations are consistent with the results in Table 5.

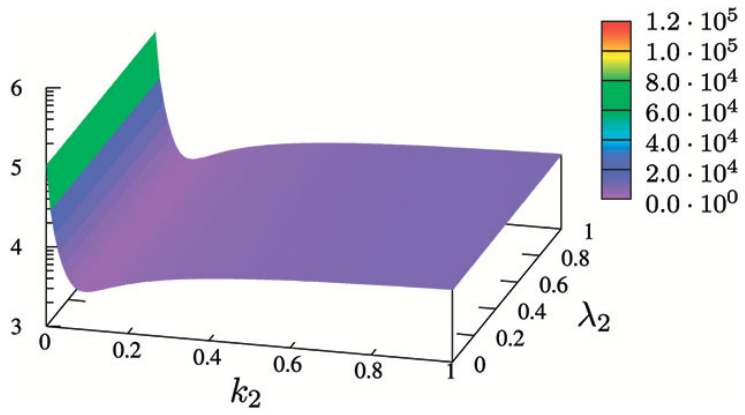

Fig. 5. Three-dimensional graph of the functional $J(\lambda_2, k_2)$ in the logarithmic scale with fixed parameters λ_1 and k_1.

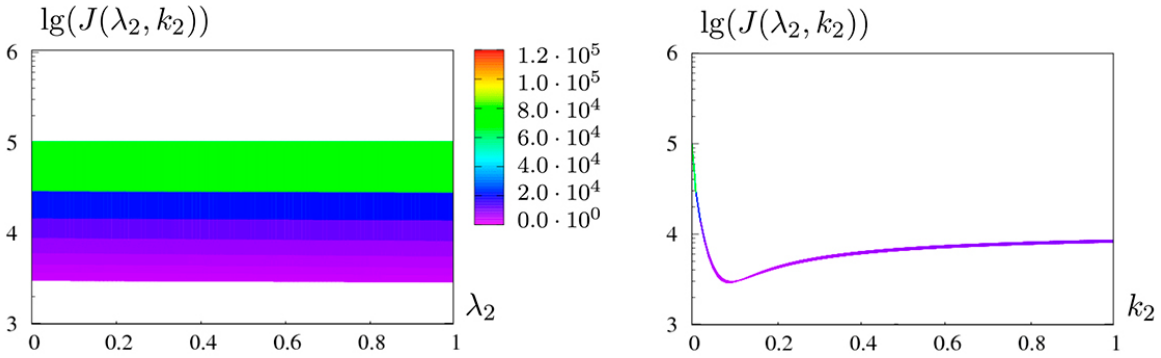

Fig. 6. The projection of the three-dimensional graph of the functional $J(\lambda_2, k_2)$ in the logarithmic scale on the plane $(\lg(J(\lambda_2, k_2)), \lambda_2)$ with fixed parameters λ_1 and k_1 (left); projection of the three-dimensional graph of $J(\lambda_2, k_2)$ in the logarithmic scale on the plane $(\lg(J(\lambda_2, k_2)), k_2)$ with fixed λ_1 and k_1 (right).

Note that for some parameters in Table 5, the relative error in estimating the average decreases with increasing variance of the approximated data. This is due to the presence of several local minima of the objective functional (see Figs. 5 and 6).

CONCLUSION

Research of identifiability of mathematical models was conducted for the systems of ordinary differential equations describing spreading the epidemic of the tuberculosis and HIV coinfection and the dynamics of HIV infection at the cellular level, using methods of sensitivity analysis and practical identifiability.

Identifiability analysis is an important step in the study of inverse problems which is necessary when developing regularizing algorithms for solving them.

The proposed methods for identifiability research allow finding nonidentifiable parameters, evaluating the required number of measurements of the inverse problem data for the existence of solutions, as well as identifying the model parameters that are most sensitive to the measurement errors.

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