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Determination of the coefficients of nonlinear ordinary differential equations systems using additional statistical information

Abstract. The study of the clinical and epidemiological features of tuberculosis combined with HIV infection (TB + HIV) is one of the priorities in the prevention of infectious diseases and is necessary to improve the quality of medical care for patients. So this article is devoted to the mathematical model of epidemiology, its' investigation and analysis. The previous works showed what identifiability analysis is and considered methods of performing them, such as orthogonal method, eigenvalue method and etc., for more precise clarification of model parameters. However, the choice of solving the inverse problem to restore unknown parameters is playing a huge role. So here was showed the combination of two numerical algorithms, as stochastic method of simulating annealing to determine the region of the global minimum and gradient method to determine the inverse problem in a region, of solving the inverse problem that will help to create effective treatment plan for the elimination and treatment of the disease.
Key words: epidemiology, inverse problems, ODE, optimization.

Introduction

Systems of nonlinear ordinary differential equations (ODE) describe processes in biology and medicine, namely, immunology, epidemiology, pharmacokinetics, sociology, economics and etc. The equations are built on the basis of the law of mass balance and operate in a closed system. The coefficients of ODE systems characterize important parameters of the immune response, the spread rate of the disease in the region, the absorption rate of drugs, etc., which cannot be determined from statistical data and need to be clarified. Specified individual parameters will allow you to create the most effective treatment plan and action plan for the elimination and treatment of the disease. One way to identify the extent of damage to the immune system, namely the parameters of the disease, the immune response, as well as determining the optimal treatment, is mathematical modeling.

According to the characteristics of the immune response, it is already possible to numerically analyze the optimal control programs for treating a disease. Example of mathematical model of epidemiology (co-infection of HIV and tuberculosis) shows studies on the identifiability of mathematical models for ODE systems, stability of inverse problems and methods for their numerical solution and computational optimization, which are necessary to develop an algorithm for regularizing the solution of inverse problems.

In [1] the deterministic model of TB dynamics was observed, they also conducted identifiability analysis by constructing sensitivity matrix to restore the identifiable parameters. The identification of parameters was conducted by solving the linear least

squares problem using the QR factorization with column pivoting.

Model

The cause of tuberculosis (TB) is a bacterium called Mycobacterium tuberculosis, which usually affects the lungs, and TB is spread by airborne droplets (coughing, sneezing, etc.). People living with HIV (PLHIV) are at much greater risk of contracting TB than HIV-negative people. If TB is not treated properly, death is possible. Tuberculosis is one of the leading causes of death among PLHIV in the world. It can manifest itself in two ways: latently infected with TB and active way of TB.

Latently infected with TB means that not all people infected with the bacteria become ill with TB. When a person is infected with TB, but has no symptoms and does not feel sick, it is considered that he has a "latent infection of TB". Such a person is not infectious and is not able to infect other people. In about 5–10% of cases, a latent infection leads to tuberculosis. This happens if an infected person does not have sufficiently strong immunity to protect against bacteria. A person with active tuberculosis feels sick; he may have the following symptoms: cough for several weeks, chest pain, blood or sputum when coughing, weakness, fatigue, weight loss, lack of appetite, chills, fever and night sweats.

Co-infection of TB and HIV is a situation where a person lives with HIV and latent or active TB at the same time. Worldwide, TB is the leading cause of death among PLHIV, as it accounts for 25% of all deaths among PLHIV. Given the detrimental effects of HIV infection on the immune system, PLHIV with TB co-infection are 20 times more likely to develop active TB [2]. In addition, it has been proven that tuberculosis increases viral replication in PLHIV and accelerates the progression of HIV, being unhealed.

A mathematical model of the epidemiology of co-infection with tuberculosis (TB) and HIV is considered [3]:

$$
\begin{cases}
\dot{S} = \Lambda - \beta c S \dfrac{(I + J_3)}{N} - \lambda \sigma S \dfrac{(J^*)}{R} - \mu S, \\[2mm]
\dot{L} = \beta c (S + T) \dfrac{(I + J_3)}{N} - \lambda \sigma L \dfrac{(J^*)}{R} - (\mu + k + r_1)L, \\[2mm]
\dot{I} = kL - (\mu + d + r_2)I, \\[2mm]
\dot{T} = r_1 L + r_2 I - \beta c T \dfrac{(I + J_3)}{N} - \lambda \sigma T \dfrac{(J^*)}{R} - \mu T, \\[2mm]
\dot{J_1} = -\beta c J_1 \dfrac{(I + J_3)}{N} + \lambda \sigma (S + T) \dfrac{(J^*)}{R} - (\alpha_1 + \mu)J_1 + r^* J_2, \\[2mm]
\dot{J_2} = \beta c J_1 \dfrac{(I + J_3)}{N} + \lambda \sigma L \dfrac{(J^*)}{R} - (\alpha_2 + \mu + k^* + r^*)J_2, \\[2mm]
\dot{J_3} = k^* J_2 - (\alpha_3 + \mu + d^*)J_3, \\[2mm]
\dot{A} = \alpha_1 J_1 + \alpha_2 J_2 + \alpha_3 J_3 - (\mu + f)A, \\[2mm]
S(0) = S_0, L(0) = L_0, I(0) = I_0, T(0) = T_0, \\[2mm]
J_1(0) = J_{1_0}, J_2(0) = J_{2_0}, J_3(0) = J_{3_0}, A(0) = A_0.
\end{cases} \tag{1}
$$

Here $S(t)$ – number of non-infected individuals, $L(t)$ – number of individuals latently infected with TB (without HIV), $I(t)$ – number of individuals with active TB (without HIV), $T(t)$ – number of individuals cured of TB (without HIV), $J_1(t)$ – the number of individuals infected with HIV (without TB), $J_2(t)$ – the number of individuals infected with HIV and latently infected with TB, $J_3(t)$ – number of individuals infected with HIV and active TB, $A(t)$ – number of individuals with AIDS. $N = S + L + I + T + J_1 + J_2 + J_3 + A$ _ total population, $R = S + L + T + J_1 + J_2$ - active population, $J^* = J_1 + J_2 + J_3$ – people infected with HIV [4].

This model contains many parameters, 6 of which are individual in each specific case and need to be clarified $q = (k, k^*, r_2, \alpha_1, \alpha_2, \alpha_3)^T$. The values of the parameters q are given in Table 1.

Table 1 – Definitions of parameters used in the model (1)

Parameter	Definition	Units	Value
k	the rate of development of active TB (without HIV)	year	0,05
k^*	the rate of development of active TB (with HIV)	year	0,25
r_2	TB treatment rate (without HIV)	human/ year	1
α_1	group HIV transition rate $J_1(t)$	year	0,1
α_2	group HIV transition rate $J_2(t)$	year	0,2
α_3	group HIV transition rate $J_3(t)$	year	0,5

Let *additional information* about system (1) be known at time points t_k of only three groups of individuals:

$$I(t_k) = I_k, J_3(t_k) = J_{3k},$$

$$A(t_k) = A_k, k = 1, \ldots, K$$

The mathematical model of co-infection of tuberculosis and HIV consists of 8 equations, but measurement data are known only about 3 of them once a year during the 5 years. That is, we have M = 3, K = 5. This model contains many parameters, 6 of which are individual in each specific case and need to be refined. Based on the analysis of identifiability carried out by one of the methods such as the orthogonal method [5], condition numbers, etc. [6], more precisely, in this work, by the method of eigenvalues [7-8], we will determine only 4 identifiable parameters $q = (k, r_2, \alpha_1, \alpha_3)^T$ from additional statistical information.

In the case of matrices of large dimensions or non-uniformly filled matrices, the eigenvalue method is unstable [9]. In such cases, it is recommended to use the method based on singular numbers [10], since it is known [11] that the condition number of the sensitivity matrix determines the convention (incorrectness) of system (2). The greater the condition number, the higher the incorrectness of the inverse problem (for the inversion of the sensitivity matrix, the use of regularization methods is required).

The values of the parameters, depending on the population, and the initial data are known are given in Table 2.

Table 2– Values of parameters and known initial data used in the model (1)

Parameter	Value	Unit
$S(0)$	430	in thousands of people
$L(0)$	3854.5	in thousands of people
$I(0)$	16.875	in thousands of people
$T(0)$	3.412	in thousands of people
$J_1(0)$	3.2757	in thousands of people
$J_2(0)$	27.7	in thousands of people
$J_3(0)$	1.4	in thousands of people
$A(0)$	0.357	in thousands of people
Λ	43	in thousands of people
N	4315.76	in thousands of people
μ	0.0143	in thousands of people
$\lambda*\sigma$	0.529	Nondimensionalized
$d*$	0.222	Nondimensionalized
f	0.997	Nondimensionalized
$\beta*c$	0.99927	Nondimensionalized
d	0.06685	Nondimensionalized

In vector form, the inverse problem is written as follows:

$$\begin{cases} \dot{X} = F(X(t), q), X(0) = X_0, \\ \qquad X_i(t_k) = \Phi_k^i. \end{cases} \qquad (2)$$

Here is the vector-function – $X = (S, L, I, T, J_1, J_2, J_3, A)$, data – $\Phi_k^i = (I_k, I_{3k}, A_k)$.

The inverse problem was reduced to the problem of minimizing the objective functional in the form:

$$J(q) = \sum_{i=1}^{3} \sum_{k=1}^{K} \left(X(t_k; q) - \Phi_k^i \right)^2 \qquad (3)$$

Due to the fact that the task of minimizing the objective functional is a multiparameter, then the determination of the global minimum requires the use of combined numerical methods – method of simulated annealing and gradient method.

Methods

Simulated annealing – general algorithmic method for solving the global optimization problem, especially discrete and combinatorial optimization. Is the one examples of Monte Carlo methods. The algorithm is created by N. Metropolis and it is based on the imitation of the physical process that occurs during the crystallization of a substance, including during annealing of metals. It is assumed that atoms are already lined up in the crystal lattice, but transitions of individual atoms from one cell to another are still permissible. It is assumed that the process proceeds at a gradually decreasing temperature. The transition of an atom from one cell to another occurs with a certain probability, and the probability decreases with decreasing temperature. A stable crystal lattice corresponds to the minimum energy of the atoms, so the atom either enters a state with a lower energy level or remains in place.

By simulating such a process, one finds a point or a set of points at which the minimum of some numerical function $F(x)$ is reached, where $x = (x_1, x_2, \dots, x_m) \in X$. The solution is figured out by sequential calculation of points $x_0, x_1, \dots$, in space X; each point, starting with x_1, "pretends" to better the solution than the previous ones. Algorithm takes point x_0 as the raw data. At each step, the algorithm (which is described below) calculates a new point and lowers the value of the "temperature" value (initially positive). The algorithm stops when it reaches a point that turns out to be at a temperature of zero.

According to the algorithm the point x_{i+1} is obtained on the basis of the current point x_i as follows. The A operator that randomly modifies the point is applied to point x_i, in result we obtain new point x^*.

The point x^* becomes a point x_{i+1} with the probability $P(x^*, x_{i+1})$, which is calculated according to the Gibbs distribution:

$$P(x^* \to x_{i+1} | x_i) = \begin{cases} 1, F(x^*) - F(x_i) < 0 \\ \exp\left(-\dfrac{F(x^*) - F(x_i)}{Q_i} \right), F(x^*) - F(x_i) \geq 0 \end{cases}$$

Here $Q_i > 0$ – elements of arbitrary decreasing, converging to zero positive sequence, which sets the analogue of the falling temperature in the crystal. The rate of decrease and the law of decrease can be set at the request of the creator of the algorithm.

The simulated annealing algorithm is similar to a *gradient descent*, but due to the randomness of the choice of an intermediate point, it should fall into local minima less often than gradient descent. The simulated annealing algorithm does not guarantee finding the minimum of the function; however, with the correct policy of generating a random point in the space X, usually, the initial approximation improves.

Gradient descent – method for finding a local extremum (minimum or maximum) of a function using motion along a gradient. To minimize the function in the direction of the gradient, one-dimensional optimization methods are used, for example, the golden section method. You can also look for not the best point in the direction of the gradient, but some better than the current one.

The easiest to implement of all local optimization methods. It has rather weak convergence conditions, but at the same time the rate of convergence is rather small (linear). The gradient method step is often used as part of other optimization methods.

The description of the method is as follows: let the objective function is $F(x): X \to R$. So the optimization problem is set as:

$$F(x) \to \min_{x \in X} F(x_j)$$

In case when maximum is needed to be find, then instead of $F(x)$ we use $-F(x)$.

The basic idea of method is to go in the direction of the fastest descent, and this direction is given by anti-gradient $-\nabla F$

$$x_{j+1} = x_j - \lambda_j \nabla F(x_j)$$

where λ_j set the velocity of gradient descent and can be chosen as
- Constant (in this case method may diverge),
- Decreasing in the process of gradient descent,
- Guaranteeing the fastest descent:

To find minimum $F(x)$ we obtain
$\lambda_j = argmin_\lambda F(x_{j+1})$
$\qquad = argmin_\lambda F(x_j - \lambda_j \nabla F(x_j))$
1. To find maximum $F(x)$ we obtain
$\lambda_j = argmax_\lambda F(x_{j+1})$
$\qquad = argmax_\lambda F(x_j - \lambda_j \nabla F(x_j))$

And the algorithm of the gradient method is look as follows:

1. Set the initial approximation and accuracy of the calculation $- x_0, \varepsilon$;
2. Calculate $x_{j+1} = x_j - \lambda_j \nabla F(x_j)$, where $\lambda_j = argmin_\lambda F(x_j - \lambda_j \nabla F(x_j))$;
3. Then check the stopping condition:
- If $|x_{j+1} - x_j| > \varepsilon$, $|F(x_{j+1}) - F(x_j)| > \varepsilon$ or $\|\nabla F(x_{j+1})\| > \varepsilon$ (choose one of conditions), then $j = j + 1$ and go to step 2.
- Otherwise $x = x_{j+1}$ and end.

The stochastic *method of simulated annealing* determines the region of the global minimum, and to determine the inverse problem in this region, the *gradient method* was used, consisting in the iterative sequence of determining the solution to the inverse problem:

$$q_{n+1} = q_n - \alpha_n J'(q_n), q_0 \in Q \qquad (4)$$

Here is the descent parameter $\alpha_n = \frac{2J(q_n)}{\|J'(q_n)\|}$ characterizes the method of steepest descent, the gradient of the objective functional $J(q_n)$ has the following form [10]:

$$J'(q_n) = -\int_0^T \Psi(t)^T F_q(X(t), q) dt \qquad (5)$$

Here the vector-function $\Psi(t)$ is the solution of the conjugate problem:

$$\begin{cases} \dot{\Psi} = -F_X^T(\dot{X}(t), q)\Psi(t), \ t \in \cup_{k=0}^K (t_k, t_{k+1}), t_0 = 0, t_{K+1} = T, \\ \Psi(T) = 0, \\ [\Psi]_{t=t_k} = 2(X(t_k; q) - \Phi_k^i), k = 1, \dots, K. \end{cases} \qquad (6)$$

Jacobi matrices have the following form:

$$F_X = \left\{ \frac{\partial F_i}{\partial X_j} \right\}_{i,j=\overline{1,N}}, F_q = \left\{ \frac{\partial F_i}{\partial X_j} \right\}_{\substack{i=\overline{1,N}, \\ j=\overline{1,M}}} \qquad (7)$$

Results

The result of solving the inverse problem for a mathematical model of co-infection with tuberculosis and HIV using a combined method of *simulating annealing* with a *gradient method* is presented in Table 3 [13-14].

Thus, effective numerical algorithms for solving inverse problems for systems of ODE (for problems of epidemiology, pharmacokinetics and immunelogy), based on a combination of stochastic and gradient methods, have been created.
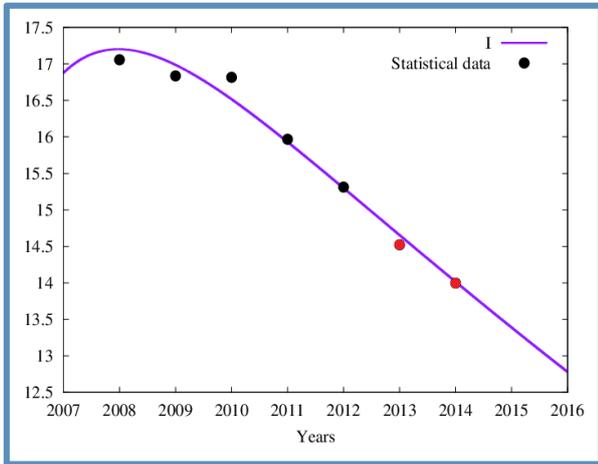
Table 3 – Solution of the inverse problem for the mathematical model of co-infection of tuberculosis and HIV

| Parameter	Relative decision error q
α_1	$1.0 * 10^{-6}$
α_2	$5.7 * 10^{-5}$
α_3	$5.3 * 10^{-6}$
k	$4.1 * 10^{-10}$

Note that for each parameter, the relative error is less than 0.001%, and the parameters α_1 and k are restored better than the others, as identifiability analysis showed. The result of solving the direct problem (1) with the found parameters is shown in Figure 1a-1c for the three measured functions. Red

dots describe statistical data that were not involved in solving the inverse problem, but are presented for comparison of the forecast using methods for solving inverse problems. It is shown that the obtained solution (solid line) is in good agreement with the real data and serves as a reliable forecast [15].

Figure 1a. – Numerical solution of the problem of the spread of co-infection of tuberculosis and HIV with specified parameters (solid line). Black dots mean data of the inverse problem, red dots – statistical data taken into account for the prediction. The number of individuals with active TB (without HIV). All values are in thousand.
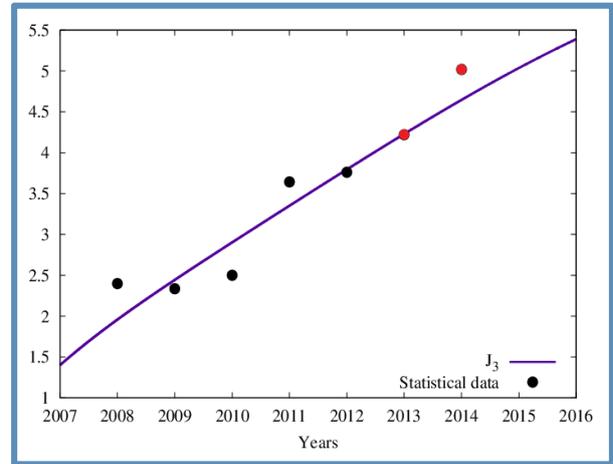
Figure 1b. – Numerical solution of the problem of the spread of co-infection of tuberculosis and HIV with specified parameters (solid line). Black dots mean data of the inverse problem, red dots – statistical data taken into account for the prediction. The number of individuals infected with HIV and the active form of TB. All values are in thousand.
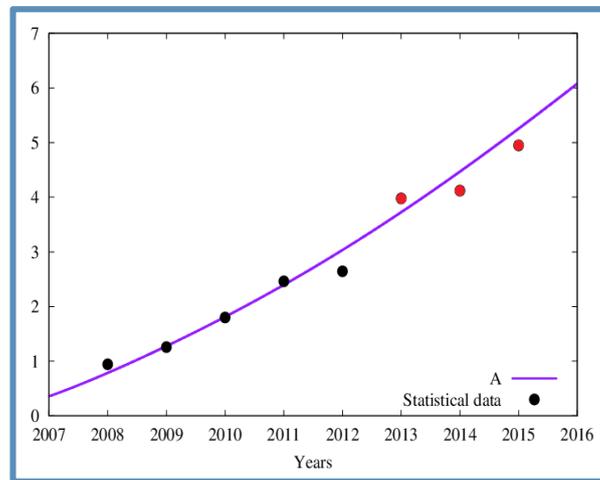
Figure 1c. – Numerical solution of the problem of the spread of co-infection of tuberculosis and HIV with specified parameters (solid line). Black dots mean data of the inverse problem, red dots – statistical data taken into account for the prediction. The number of individuals with AIDS. All values are in thousand.

Conclusion

The research and analysis of the problem arising in bio-medicine has been carried out, the theoretical aspects of this task have been built, including identifiability analysis, which is an important step in the study of the mathematical model, and is necessary for the correct solution of the inverse problem, since it shows the uniqueness, existence and / or stability of the solution .

New combined numerical algorithms for solving the direct and inverse problems of epidemiology have been built. Efficient numerical algorithms for solving inverse problems for systems of ODE (for problems of epidemiology, pharmacokinetics and immunology), based on a combination of statistical and gradient methods, have been created.

Numerical algorithms for solving the problems of determining the coefficients of nonlinear ODE systems using additional statistical information were developed and analyzed.

Thus, the conducted scientific work opens up new directions for the development of research in science and technology, namely, the refinement of mathematical models will improve the prognosis of the disease or the development of the epidemic, which would entail the need for a plan of measures for treating patients and eliminating the consequences of the disease / epidemic.

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