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INVERSE PROBLEMS OF IMMUNOLOGY AND EPIDEMIOLOGY

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Abstract. A parameter identification problem (inverse problem) for some mathematical models of HIV dynamics and tuberculosis epidemics with experimental observations is investigated. The inverse problems are reduced to a minimization problem. The optimization problem is solved with the help of stochastic methods: a genetic algorithm and fast simulated annealing. The results of numerical calculations are presented.

Key words: Inverse problem, ordinary differential equations, optimization problem, parameter identification, genetic algorithm, simulated annealing.

AMS Mathematics Subject Classification: 49M30, 65L09, 92B05.

1 Introduction

Many mathematical models of biological processes (of pharmacokinetics, immunology, epidemic spread, *etc.*) can be described by systems of nonlinear ordinary differential equations (ODEs). The equations in the system being investigated (varying in number from two to several tens) are determined by a model. In the general case, the biological models have specific parameters describing model characteristics (coefficients of a system of differential equations $\dot{X} = PX$, where P is a matrix in the linear models). They have to be identified to obtain important information about the susceptibility to specific drugs, diseases, immune response, epidemic spread, *etc.*Those parameters can be estimated (or sometimes uniquely determined) using some additional information about the biological processes (concentration of drugs, viruses, antigens, infected patients, *etc.*). The problem of determining the biological parameters using such additional information is said to be an inverse problem. In the present paper, some inverse problems for mathematical models of cellular HIV dynamics and tuberculosis epidemics are investigated.

The HIV was discovered independently in 1983 in two laboratories: at the Pasteur Institute in France and the National Institute of Cancer in the US. A.S. Perelson et al. [1], B.M. Adams et al. [2], and G. Bocharov et al. [3] investigated the effects of the virus on the human body. Currently, there are many mathematical models describing the dynamics of an HIV infection which contains different types of immune cells. The early linear models proposed in [4, 5, 6, 7] are approximations to more realistic nonlinear models for viral and infected cell decay, and thus are applicable, at best, only for short periods of time. Since these models have been useful in characterizing the short-term dynamics of the HIV infection after therapy, several researchers attempted to use these models to estimate the time of virus eradication in individuals. Such predictions need

time periods that are beyond those needed to appropriately approximate the nonlinear dynamics by a linear model.

To model data over longer periods of time and make long-term predictions, nonlinear mathematical models are necessary. The authors of paper [8] reason that more complex nonlinear models are needed to accurately describe the long-term viral decay.

The viral production of cells infected with HIV depends on the "age" (e.g., the time elapsed from the start of infection) of the infected cells. There are multiple biological aspects of this function of age. The intra-cellular delays due to viral reverse transcription, integration, transcription, and virion formation are described by J.E. Mittler et al. [9] extending the work in [7]. J.E. Mittler allows the intra-cellular delays to vary across the cells, and estimates these delays to be more significant than the pharmacological delays associated with drug absorption.

The above mathematical models of HIV are characterized by parameters that describe the properties of immunity and disease. It is necessary to estimate these parameters with known additional information to formulate an optimal treatment plan. B.M. Adams et al. [2] investigate the problem of parameter identification for a mathematical model of HIV dynamics. Using the least squares method, they obtained two parameters. In the present paper, we consider the mathematical model for HIV dynamics from paper [2]. For this model we solve the parameters identification problem by using a genetic algorithm. We obtain four parameters. And it is shown that the relative accuracy error of the four-parameter identification is sufficiently small for a good mathematical model that has a solution close to additional measurements.

A second mathematical model under consideration describes a tuberculosis epidemic in the Russian Federation. An epidemic of tuberculosis (TB) is typically accompanied by quantitative and qualitative changes in the character of this disease that are specific for the region under study. It is necessary to make a prediction of the epidemic spread in a particular region to create an action plan to identify and treat the patients in this region. Mathematical simulation, namely, the development of a specific mathematical model describing the process of infection propagation in the population, is one of the most efficient methods of epidemic spread prediction.

Hans Waaler et al. [10, 11, 12, 13, 14, 15] were the first to construct and develop an integral mathematical model of tuberculosis epidemiology (with a description of the processes of infection, development of latent infection, disease, and its further spread). In the 1970s-80s the detection and treatment of the patients infected with tuberculosis were studied within TSRU (Tuberculosis Surveillance Research Unit) [16]. In later years, a research team headed by Sally M. Blower was engaged in the development of models of natural dynamics of tuberculosis, medical intervention, interaction with other deadly diseases, and qualitative estimation of their parameters on the basis of statistical data, etc.[17, 18, 19, 20, 21]. Several "global" tuberculosis spread models describing both the processes of spread, chemoprophylaxis, detection and treatment programs, etc. were developed in the late 20th century [22, 23, 24]. These studies considered mainly the structure of mathematical models and the results of numerical experiments. The model parameters determining the tuberculosis spread process were typically taken from the literature. The predictions and recommendations on how to organize anti-tuberculosis programs were based on averaged values and did not take

into account the parameter variations and regional peculiarities.

Recently, new models based on previous studies and real data and taking into account the peculiarities of populations of Russian regions, have been created [25, 26]. In the present paper, a convenient method of model set-up combined with numerical methods for some specific populations is proposed. With statistical data processed for several preceding years, the algorithm yields the degree of deviation from the mean values of parameters of the infection for each individual population. Thus, public health organizations can predict the development of epidemics of an infectious disease in this region by comparing the results of simulations with the available historic data.

2 Inverse problem statement

Let us consider a Cauchy problem for the system of nonlinear ODEs

$$\dot{X} = P(X(t), \Theta), \quad X(0) = X^0, \quad t \in (0, T),\ T > 0. \tag{1}$$

Here $X(t) = (X_1(t), \ldots, X_N(t))^{\mathrm{T}}$ is the N-vector of model variables, Θ is a parameter, an M-vector equal to $(\Theta_1, \ldots, \Theta_M)^{\mathrm{T}} \in \mathcal{P}$, $\mathcal{P} := \{p \in \mathbb{R}^M : p_m \geq 0,\ m = 1, \ldots, M\}$ is the space of parameters being considered, $P(X(t), \Theta) = (P_1(X(t), \Theta), \ldots, P_N(X(t), \Theta))^{\mathrm{T}}$ is a vector-function $P_n(X(t), \Theta) : C^2(0, T) \to C^2(0, T),\ n = 1, \ldots, N,$ // $X^0 = (X_1^0, \ldots, X_N^0)^{\mathrm{T}}$ is the N-vector of initial data.

The inverse problem for the direct problem (1) is in determining the vector of model parameters and the initial data $q = (\Theta, X^0)^{\mathrm{T}}$ from the given function P and some additional information about the vector $X(t; q)$:

$$X_n(t_k; q) = \Phi_n(t_k), \quad t_k \in (0, T), \quad k = 1, \ldots, K_n,\ n = 1, \ldots, N. \tag{2}$$

Here $\Phi_n(t_k) := \Phi_n^{(k)} = (\Phi_n^{(1)}, \ldots, \Phi_n^{(K_n)})^{\mathrm{T}}$ is the vector of inverse problem data of dimension $K := K_1 + \ldots + K_N$. The vector $X(t; q)$ describes the concentration of drugs, glucose, and insulin in blood and plasma (in pharmacokinetics problems); the concentration of viruses, immune system parameters (plasma cells, antibodies, macrophages, etc.), characteristics of target organ affection, and others (in immunology problems); the number of infection carriers, the number of noninfectious patients, *etc.* (in epidemiology problems). The vector $\Phi = (\Phi_1^{(1)}, \ldots, \Phi_1^{(K_1)}, \ldots, \Phi_N^{(1)}, \ldots, \Phi_N^{(K_N)})^{\mathrm{T}}$ is determined from blood and urine data at times t_k, $k = 1, \ldots, K$.

Let us define an operator for the inverse problem (1), (2) as follows: $A : q \in \mathcal{P} \to \Phi \in \mathbb{R}^K$. Thus, the inverse problem (1), (2) can be written in operator form as $A(q) = \Phi$.

$A(q) = \Phi$ will be solved by minimizing the following misfit function:

$$J(q) = \|A(q) - \Phi\|^2 = \sum_{k=0}^{K} |X(t_k; q) - \Phi^{(k)}|^2, \tag{3}$$

that is, solving the problem $A(q) = \Phi$ is reduced to solving the problem of finding $\min\limits_q J(q)$.

In paper 2009 [27] by H.W. Engl et al., the inverse problem (1), (2) was numerically investigated for well-posedness with gradient methods (Levenberg-Marquardt and Gauss-Newton ones) using A.N. Tikhonov's regularization in the numerical calculations. In paper [28] authors derive the formula for the gradient of misfit function (3) connected with adjoint problem and apply Landweber iteration approach in numerical experiments. In the present paper, for the inverse problem (1), (2) an optimization algorithm based on a stochastic method, namely, a genetic algorithm and a very fast simulated annealing method, will be presented.

3 Numerical methods

3.1 Genetic algorithm

The problem of functional minimization (3) can be solved by linear programming methods and gradient methods of zero [29], first [30], and higher orders. A general drawback of the deterministic methods is that the initial approximation must be close to the exact solution. It is often a difficult task. We use a stochastic method (genetic algorithm) [31] for solving the inverse problem described above. This method is as follows:

1. ***Choosing an initial population***: choose arbitrary values of the N vectors of parameters $q^i = (q_1^i, \ldots, q_M^i)^T$, $i = 1, \ldots, N$ from the admissible intervals. For each q^i, calculate the misfit function $J(q^i)$.

2. ***Selecting***: choose N pairs of parents. The probability that a member of the population falls into a pair is high if the value of its misfit function has low level. The probability that the i-th member of the population falls into a pair can be calculated by using the following formula: $P^i = \frac{J(q^i)}{\sum\limits_{i=1}^{N} J(q^i)}$.

3. ***Crossing***: crossing each pair (q^i, q^j), $i, j = 1, \ldots, N$ by crossing-over, we get N descendants. For this purpose, we choose two random numbers: one is a random integer $Q \in [1, N-1]$, and the other is a random integer R which can be either 1 or 2. The number Q characterizes the dividing line of the parents, the number R shows which part (left or right) from the dividing line descendant inherits from the mother and father.

   - If $Q = s$, $R = 1$, $s \in [1, N-1]$:
     mother: $(q_1^i, \ldots, q_s^i, |q_{s+1}^i, \ldots, q_M^i)^T$, father: $(q_1^j, \ldots, q_s^j, |q_{s+1}^j, \ldots, q_M^j)^T \longrightarrow$
     descendant: $(q_1^i, \ldots, q_s^i, |q_{s+1}^j, \ldots, q_M^j)^T$.
   - If $Q = s$, $R = 2$, $s \in [1, N-1]$:
     mother: $(q_1^i, \ldots, q_s^i, |q_{s+1}^i, \ldots, q_M^i)^T$, father: $(q_1^j, \ldots, q_s^j, |q_{s+1}^j, \ldots, q_M^j)^T \longrightarrow$
     descendant: $(q_1^j, \ldots, q_s^j, |q_{s+1}^i, \ldots, q_M^i)^T$.

4. ***Mutating***: make random changes in the posterity, i.e.

   - choose a random volume A of descendants to which the mutation will be applied. Here A is a random integer from 1 to N;

- Then choose random integers $B_i \in (1, N), i = 1, \ldots, A$. $B_i, i = 1, \ldots, A$ are the item numbers of descendants that will mutate;
- For each mutating descendant B_i, choose a random volume $C_{B_i}, i = 1, \ldots, A$ of mutating elements. Here C_{B_i} is a random integer from 1 to M;
- Then choose random integers $D_k \in (1, M), k = 1, \ldots, C_{B_i}, i = 1, \ldots, A$, which characterize the item number of mutating elements and replace each mutating element by a new random value from the allowable period.

5. ***Forming a new generation***: Choose the fittest member among the parents and descendants, i.e. choose the member that has the lowest value of the misfit function $J(q^i)$. Also, choose a few "lucky ones" of the generation members that badly minimize the functional. They will bring diversity to the subsequent generations.

6. ***Checking the exit condition***:

   - $J(q^i) < \Delta$. Here $J(q^i)$ is the lowest value of the misfit function in the population, Δ is a given number. In the paper, as the value of Δ we take 0.0001.
   - The smallest value of the misfit function in the population changes by less than 10^{-8} within 500 consecutive iterations.

   If at least one of the conditions is satisfied, the resulting population is found. Choose from the population a vector with the lowest value of the misfit function. If not, go to step 2.

If the genetic algorithm is stuck in a local minimum, the step of mutation will help to get out of it. As practice shows, we can find a global minimum using the genetic algorithm for the optimization problem. It is important when working with real data.

3.2 Very fast simulated annealing method

A very fast simulated annealing method consists in finding a global minimum using an ordered random search constructed by analogy with the process of crystalline structure formation with minimal energy under quenching [32].

The very fast simulated annealing method with a coefficient c for faster decrease in a temperature $T(j+1) = cT(j)$ [32] (also called the "quenching" method) is used to find the global minimum domain of the objective functional. In our case, the temperature $T(j)$ is some function of a natural argument with values in $\mathbb{R}^m$ which controls the iteration number.

Assume that each parameter $q_i,\ i = 1, \ldots, m$, lies in some interval $q_i \in [A_i, B_i],\ i = 1, \ldots, m$.

Quenching method algorithm:

1. Set maximum and minimum values: $T_0 = T_{max}$ and T_{min}.

2. Choose arbitrarily a vector $q_{(0)} \in \mathbb{R}^m : q_{(0)_i} \in [A_i, B_i]$, and calculate the functional value $J(q_{(0)})$.

3. Let the values $q_{(j)}$ and $J(q_{(j)})$ be found. The calculation of $q_{(j+1)}$ is as follows:

4. Specify m independent random numbers $\alpha_i, i = 1, \ldots, m$, uniformly distributed in the interval [0, 1]. Calculate a new vector q' by the rule

$$q'_i = q_{(j)_i} + z_i(B_i - A_i),$$

where z_i is a random quantity of the form

$$z_i = sgn(\alpha_i - 0.5)T(j)((1 + 1/T(j))^{|2\alpha_i - 1|} - 1).$$

5. Calculate the functional value at the new point, $J(q')$:

   (a) If $\Delta J = J(q') - J(q_{(j)}) < 0$, go to step 7.

   (b) If $\Delta J = J(q') - J(q_{(j)}) > 0$, go to step 5.

6. Calculate the probability of choosing the new approximation

$$p(\Delta J, T(j)) = \exp(-\Delta J/T(j)).$$

7. Specify a random number α uniformly distributed in the interval [0,1].

   (a) If $\alpha < p(\Delta J, T(j))$, go to step 7.

   (b) If $\alpha > p(\Delta J, T(j))$, go to step 3.

8. Choose a new point $q_{(j+1)} = q'$.

9. Decrease $T(j + 1) = cT_0 \exp(-k^{1/m}d), d > 0$ is a parameter of the "quenching" method.

   (a) If $T(j + 1) < T_{min}$, end of iteration.

   (b) If $T(j + 1) > T_{min}$, go to step 3.

Zhiglyavskii A.A. [33] proved a general theorem of statistical convergence of the global optimization methods to the global minimum domain. A proof of this theorem for the very fast quenching method is presented in [33, 34, 35, 36].

4 Examples

4.1 Inverse problem for a mathematical model of HIV dynamics

A mathematical model of HIV dynamics [2] can be described by the following system of nonlinear differential equations:

$$\begin{cases} \dot{T}_1 = \lambda_1 - d_1 T_1 - k_1 V T_1, \\ \dot{T}_2 = \lambda_2 - d_2 T_2 - k_2 V T_2, \\ \dot{T}_1^* = k_1 V T_1 - \delta T_1^* - m_1 E T_1^*, \\ \dot{T}_2^* = k_2 V T_2 - \delta T_2^* - m_2 E T_2^*, \qquad t \in (0, T), \\ \dot{V} = N_T \delta (T_1^* + T_2^*) - cV - [\rho_1 k_1 T_1 + \rho_2 k_2 T_2] V, \\ \dot{E} = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E + \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E \end{cases} \tag{4}$$

The initial conditions for mathematical model (4) are:

$$T_1(0) = 500000,\ T_2(0) = 4800,\ T_1^*(0) = 5000,\ T_2^*(0) = 10,\ V(0) = 10000,\ E(0) = 15. \tag{5}$$

Here (T_1, T_1^*) are uninfected and infected T-lymphocytes, respectively, (T_2, T_2^*) are uninfected and infected macrophages, V is a free virus, and E are immune effectors.

The mathematical model (4) contains 19 parameters that characterize some features of immunity and disease: λ_1, λ_2, d_1, d_2, k_1, k_2, δ, m_1, m_2, N_T, c, ρ_1, ρ_2, λ_E, b_E, d_E, K_b, K_d, δ_E. In [37] A.S. Perelson shows that the majority of these parameters are defined accurately, and only four of them, k_1, k_2, λ_1, λ_2, need to be clarified: k_1, k_2, the infection rates of CD4 T-lymphocytes and macrophages, λ_1, λ_2, the T-lymphocytes and macrophages production (source) rates. These parameters are individual for each person. It is necessary to clarify these four parameters for each patient.

The parameter identification problem (inverse problem) for the mathematical model (4) with the initial conditions of the form (5) consists in determining the parameter vector $q = (k_1, k_2, \lambda_1, \lambda_2)^T$ with known additional information about the concentrations of T-lymphocytes in the organism $T_1 + T_1^*$, free virus V and immune effectors E in a fixed time $t_k, k = 1, \dots, K$:

$$T_1(t_k) + T_1^*(t_k) = \Phi_1(t_k),\ V(t_k) = \Phi_2(t_k),\ E(t_k) = \Phi_3(t_k), \quad k = 1, \dots, K. \tag{6}$$

The inverse problem (4)-(6) can be reduced to a problem of minimizing the misfit functional $J_1(q)$:

$$J(q) = \sum_{k=1}^{K} ((T_1(t_k; q) + T_1^*(t_k; q)) - \Phi_1(t_k))^2 + (V(t_k; q) - \Phi_2(t_k))^2 + \\ + (E(t_k; q) - \Phi_3(t_k))^2. \tag{7}$$

The misfit functional $J(q)$ characterizes the degree of deviation of the model data from the experimental data. Here $T_1(t_k; q) = T_1(t_k), T_1^*(t_k; q) = T_1^*(t_k), V(t_k; q) = V(t_k), E(t_k; q) = E(t_k)$ is the solution of the Cauchy problem (4)-(5) for a set of parameters q at a fixed point t_k.

4.1.1 Numerical solution of the inverse problem

In the present paper we use model data for solving the inverse problem. Let us consider a time period $T = 100$ days and construct a partition of the domain $(0, T)$: $\omega_1 = \{t_j : t_j = jh_t, h_t = T/N_t, j = 1, \ldots, N_t, N_t = 10000\}$. To determine the vector of parameters $q = (k_1, k_2, \lambda_1, \lambda_2)^T$ for the problem (4)-(6), let us construct synthetic data (6) using a standard set of parameters for the infected patient [2]. To do this, let us choose an exact vector of parameters as follows: $q_{ex} = (k_1^{ex}, k_2^{ex}, \lambda_1^{ex}, \lambda_2^{ex})^T = (10^4, 31.98, 8{*}10^{-7}, 10^{-4})^T$.

In the present paper, we analyze the frequency of measurements of the concentrations of T-lymphocytes $(T_1 + T_1^*)$, free virus (V) and immune effectors E. Using the genetic algorithm, we obtain values of the relative error $|q - q_{ex}|/|q_{ex}|$ for the frequency of measurements $K = 3$ (the measurements are carried out once a month), $K = 7$ (the measurements are carried out once every two weeks), and $K = 14$ (the measurements are carried out once a week). It is shown that if we increase the number of measurements, the average (arithmetic mean) relative error decreases. Based on this consideration, we assume that the measurements of concentrations 6 are performed with a frequency of once a week. Thus, we have $K = 14$ measurements of the concentrations of T-lymphocytes, free virus and immune effectors during 100 days.

In Figures 1, 2, the relative error $|q_{ex} - q_n|/|q_n|$ (Fig. 1) versus the number of iterations n and the misfit function $J(q_n)$ (Fig. 2) versus the number of iterations n are presented. By increasing the number of iterations, the relative error and the misfit functional decrease. This shows that the method is convergent. Since the inverse problem is reduced to minimizing the functional $J(q_n)$, the curve (Fig. 3) of dependence between the relative error and the misfit function is important for us. This curve shows that with decreasing functional the relative error decreases too. It means that if we reduce $J(q_n)$, the parameters q_n obtained are close to the exact values q_{ex}.

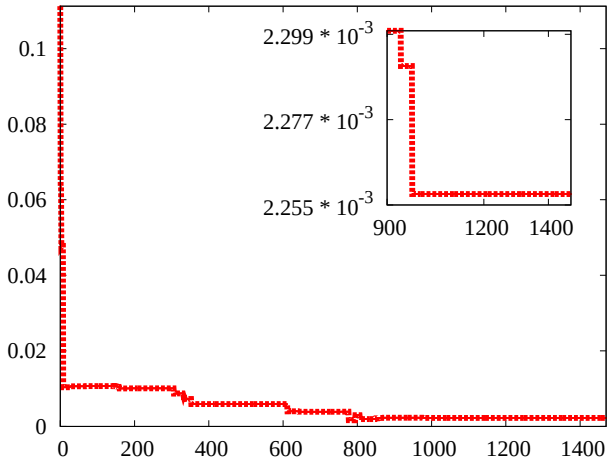

Figure 1: Relative error $|q_{ex} - q_n|/|q_n|$ versus the number of iterations n.

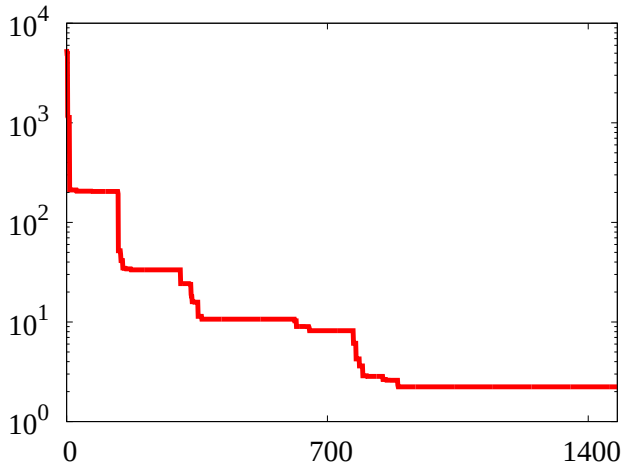

Figure 2: Misfit functional $Log(J(q_n))$ versus the number of iterations n.

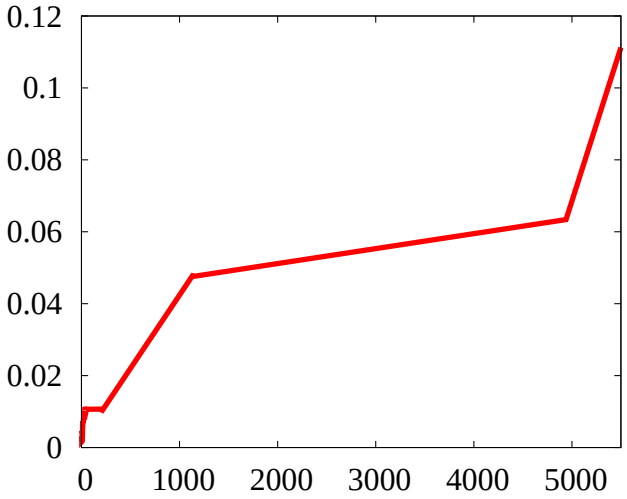

Figure 3: Misfit function $J(q_n)$ versus the relative error $|q_{ex} - q_n|/|q_n|$.

In Table 1 the numerical results for the parameter identification problem are presented. These results were obtained using the genetic algorithm. It can be seen that the two parameters λ_1, k_1 are determined accurately enough, and the other two, λ_2 and k_2, have relative errors of about 10 %.

In Figure 4, the direct problem solutions (4) (solid lines) for the thus-obtained parameters and measurements of concentrations (6) at fixed times (points) are presented. The curves show that the relative accuracy error of the four parameters identification is sufficiently small for a good mathematical model that has a solution close to the additional measurements of CD4 T-lymphocytes (T1+T1*), immune effectors E, and free viruses V.

Note that additional information (6) of the concentrations of T-lymphocytes, free

Table 1: Numerical solution of the parameters identification problem for mathematical model of HIV-dynamics (4)

	Exact parameters, q_{ex}	Approximate parameters, q	Relative error, $\lvert q^i_{ex} - q^i\rvert/\lvert q^i_{ex}\rvert$	Common relative error, $\lvert q_{ex} - q\rvert/\lvert q_{ex}\rvert$	Misfit functional, $J_1(q)$
$\lambda_1(\frac{cells}{ml\cdot days})$	10^4	$1.0015 \cdot 10^4$	0.00149	0.00226	2.23494
$\lambda_2(\frac{cells}{ml\cdot days})$	31.98	32.7871	0.02527	0.00226	2.23494
$k_1(\frac{ml}{virions\cdot days})$	$8 \cdot 10^{-7}$	$7.9802 \cdot 10^{-7}$	0.00248	0.00226	2.23494
$k_2(\frac{ml}{virions\cdot days})$	10^{-4}	$1.1693 \cdot 10^{-4}$	0.16933	0.00226	2.23494

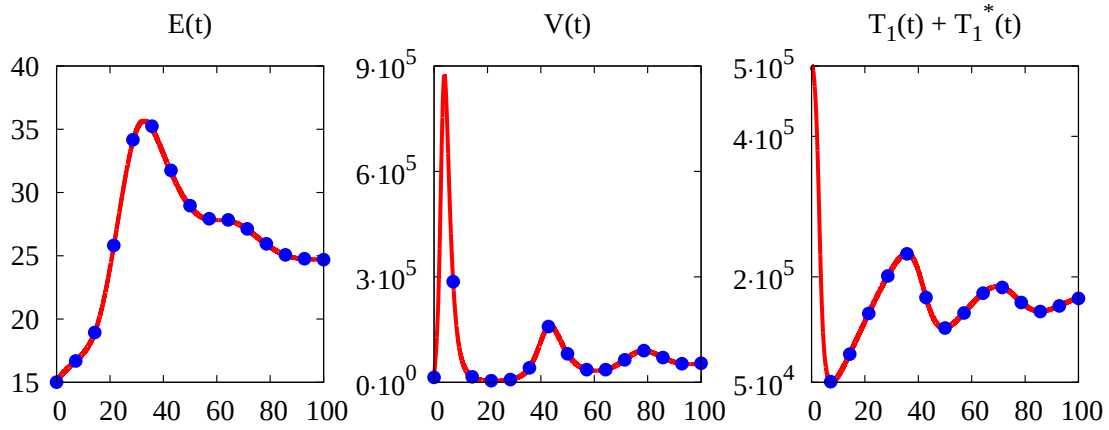

Figure 4: Concentrations of immune effectors $E(t)$ (left), free virus $V(t)$ (center), and T-lymphocytes $T_1(t) + T_1^*(t)$ (right). Points on the curves are measurements of concentrations (6) at fixed times

virus and immune effectors can be obtained from blood tests. It is known that above measurements have a Gaussian noise of about 10%. Let us present the numerical results of the inverse problem solution (4)-(6) if we have additional (6) measurements with Gaussian noise of 10%. In table 2 numerical results of inverse problem are presented. As in the previous case we obtain fairly accurate values only of the parameters λ_1 and k_1. Note, that the second and forth equations in mathematical model (4) for functions $T_2(t)$ and $T_2^*(t)$ respectively depend on parameters λ_2 and k_2. But additional information (6) for inverse problem (4)-(6) is known only for functions $T_1(t) + T_1^*(t)$, $V(t)$ and $E(t)$. That is the main reason of a big error in reconstruction of parameters λ_2 and k_2. For better accuracy in λ_2 and k_2 we need to obtain an additional information about any combinations of uninfected and infected macrophages.

In Figure 5, the direct problem solutions (4) (solid lines) for the thus-obtained parameters and noised measurements of concentrations (6) at fixed times (points) are

presented. The curves show that the common relative accuracy error of the four parameters identification is sufficiently small for a good mathematical model that has a solution quite close to the additional noised measurements of CD4 T-lymphocytes $(T_1 + T_1^*)$, immune effectors E, and free viruses V.

Table 2: Numerical solution of the parameters identification problem for mathematical model of HIV-dynamics (4) when we have Gaussian noise of 10% in data.

	Exact parameters, q_{ex}	Approximate parameters, q	Relative error, $\lvert q^i_{ex} - q^i \rvert / \lvert q^i_{ex} \rvert$
$\lambda_1(\frac{cells}{ml \cdot days})$	10^4	$0.0989 \cdot 10^4$	0.0107
$\lambda_2(\frac{cells}{ml \cdot days})$	31.98	43.7049	0.3666
$k_1(\frac{ml}{virions \cdot days})$	$8 \cdot 10^{-7}$	$7.9949 \cdot 10^{-7}$	0.0006
$k_2(\frac{ml}{virions \cdot days})$	10^{-4}	$0.5024 \cdot 10^{-4}$	0.4976

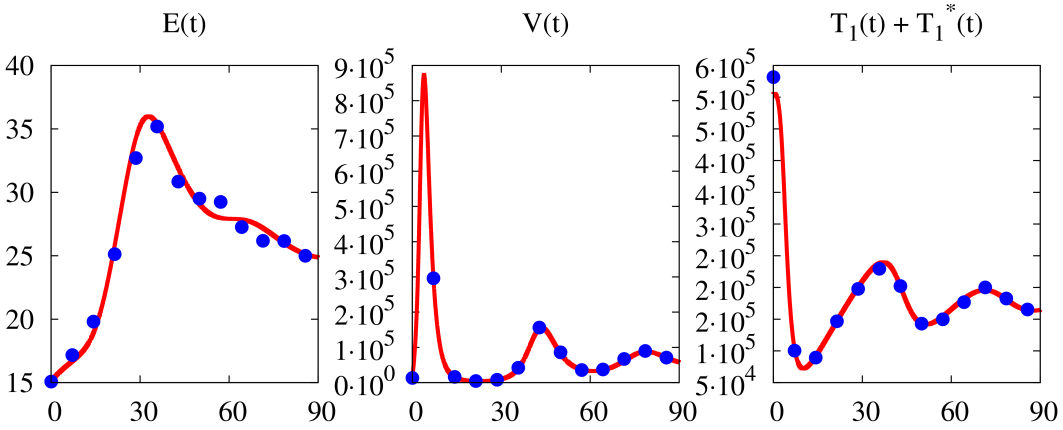

Figure 5: Concentrations of immune effectors $E(t)$ (left), free virus $V(t)$ (center), and T-lymphocytes $T_1(t) + T_1^*(t)$ (right). Points on the curves are noised measurements of concentrations (6) at fixed times.

Note that the program runtime on a personal computer with processor Intel (R) Core (TM) i3 2.13GHz and 4GB of RAM is about 5 minutes.

4.2 Inverse problem for a mathematical model of tuberculosis transmission with control programs

Consider a Cauchy problem for the following mathematical model of tuberculosis spread developed by a group of Australian researchers [38] taking into account the treatment and appearance of new tuberculosis strains during the period of treatment:

$$
\begin{cases}
\frac{dS_A}{dt} = (1-l)\pi N - (\lambda + \lambda_m + \mu)S_A, \\
\frac{dS_B}{dt} = l\pi N + \varphi T + \varphi_m T_m - (\lambda_d + \lambda_{dm} + \mu)S_B, \\
\frac{dL_A}{dt} = \lambda S_A + \lambda_d(S_B + L_B + L_{Bm}) - (\varepsilon + k + \mu)L_A, \\
\frac{dL_{Am}}{dt} = \lambda_m S_A + \lambda_{dm}(S_B + L_B + L_{Bm}) - (\varepsilon + k + \mu)L_{Am}, \\
\frac{dL_B}{dt} = kL_A + \gamma I - (\lambda_d + \lambda_{dm} + \nu + \mu)L_B, \\
\frac{dL_{Bm}}{dt} = kL_{Am} + \gamma I_m - (\lambda_d + \lambda_{dm} + \nu + \mu)L_{Bm}, \\
\frac{dI}{dt} = \varepsilon L_A + \nu L_B + (1-\nu)\omega T - (\gamma + \delta + \mu_i)I, \\
\frac{dI_m}{dt} = \varepsilon L_{Am} + \nu L_{Bm} + \nu\omega T - (\gamma + \delta_m + \mu_i)I_m, \\
\frac{dT}{dt} = \delta I - (\varphi + \omega + \mu_t)T, \\
\frac{dT_m}{dt} = \delta_m I_m - (\varphi_m + \omega + \mu_t)T_m, \\
S_A(0) = S_{A_0},\ S_B(0) = S_{B_0},\ L_A(0) = L_{A_0},\ L_{Am}(0) = L_{Am_0}, \\
L_B(0) = L_{B_0},\ L_{Bm}(0) = L_{Bm_0},\ I(0) = I_0,\ I_m(0) = I_{m_0}, \\
T(0) = T_0,\ T_m(0) = T_{m_0}.
\end{cases}
\tag{8}
$$

Here

$$
\lambda = \beta\rho(I + oT)/N,\ \lambda_m = \beta_m\rho(I_m + oT_m)/N,
$$
$$
\lambda_d = \chi\beta\rho(I + oT)/N,\ \lambda_{dm} = \chi\beta_m\rho(I_m + oT_m)/N.
$$

In equation (8), the population is divided into sensitive unvaccinated (S_A) and vaccinated (S_B) patients, latent infection carriers, also having the MDR-TB strain (with index m), with fast (L_A, L_{A_m}) and slow (L_B, L_{B_m}) development of the active form of the disease, patients with open form of the disease under treatment (T, T_m) and not under treatment (I, I_m).

Some parameters characterizing the peculiarities of the population and the disease for equations (8) are listed in Table 3.

This is a system of first-order nonlinear ordinary differential equations (1). Here $X = (S_A, S_B, L_A, L_{Am}, L_B, L_{Bm}, I, I_m, T, T_m)^T$ is the vector of unknown functions, $X_0 = (S_{A_0}, S_{B_0}, L_{A_0}, L_{Am_0}, L_{B_0}, L_{Bm_0}, I_0, I_{m_0}, T_0, T_{m_0})^T$ is the vector of initial data, F is a given vector-function, and $q = (\pi, \mu, \varphi, \varphi_m, \varepsilon, k, \gamma, \nu, \eta, \omega, \delta, \delta_m, \mu_i, \mu_t, \beta, \beta_m, \chi, \rho, o, l)^T$ is the vector of the model parameters to be reconstructed.

Assume that at times t_k we know the following additional information about the functions $X_{l_1}(t), \ldots, X_{l_d}(t)$, where $\{l_1, \ldots, l_d\} \subset \{1, \ldots, 10\}$:

$$
\begin{aligned}
&X_{l_1}(t_k) = X_{l_1}^k,\ k = 1, ..., K_{l_1}, \\
&\ldots \\
&X_{l_d}(t_k) = X_{l_d}^k,\ k = 1, ..., K_{l_d}.
\end{aligned}
\tag{9}
$$

This is a problem of reconstructing the parameters of the mathematical model of equations (8)-(9). It is required to determine a vector of 20 parameters, $q =$

Table 3: Parameters of equations (8) for, as an example, some countries of the Asian–Pacific region.

Symbol	Description	Units	Size
Π	inflow of young people to model population	people/year	depends on population type
N	total population size	people	depends on population type
$1/\mu$	average life expectancy	year	depends on population type
φ	tuberculosis treatment rate	people/year	2
φ_m	MDR-TB treatment rate	people/year	0.5
ε	disease early progression rate	year	0.129
k	transition rate to disease late progression	year	0.821
γ	spontaneous self-recovery rate	year	0.63
ν	development rate of active disease form under endogenous activation	year	0.075
η	probability of MDR-TB strain development during treatment	-	0.035
ω	reinfection rate	people/year	0.25
δ	detection rate of individuals with active TB form	people/year	0.72
δ_m	detection rate of individuals with active MDR-TB form	people/year	0.035
μ_i	tuberculosis mortality without treatment	year	0.37
μ_t	tuberculosis mortality during treatment	year	$0.5\mu_i$
β	contagiousness parameter	-	depends on population type
β_m	contagiousness parameter for MDR-TB	-	0.7β
χ	partial immunity parameter	-	0.49
ρ	infection fraction	-	0.7
o	transmissibility parameter of individuals during treatment	-	0.6
l	BCG vaccination rate	-	0.65

$(q_1, \ldots, q_{20})^T \in \mathbb{R}^{20}$, from the additional information about the solution of the direct problem:

$$\Phi_i(t_k) \ := \Phi_i^{(k)} = \left(X_{l_i}^1, \ldots, X_{l_i}^{K_{l_i}}\right)^T \in \mathbb{R}^{K_{l_i}},\ i = 1, \ldots, d.$$

The inverse problem (8)-(9) is reduced to finding a minimum of the objective functional

$$J(q) = \sum_{i=1}^{d} \sum_{k=1}^{K_{l_i}} |X_{l_i}(t_k; q) - \Phi_i^{(k)}|^2. \tag{10}$$

This optimization problem is solved by the very fast simulated "quenching" method.

4.2.1 Numerical calculations

Now let us solve the problem of reconstructing the parameters of equation (1) for the model of equation (8).

As a model population, consider the Siberian Federal District (SFD) population. According to the Russian legislation, infant BCG (Bacillus Calmette-Guerin) vaccination is obligatory for the Russian citizens with morbidity rates exceeding 80 cases per 100 thousand , and most population of the SFD is vaccinated at the preschool ages. Therefore, the coefficient l in Table 3 for the SFD is taken equal to 1, and $S_A(0) = 0$. Since the Cauchy problem has a unique solution [39] and $S_A \equiv 0$ under these conditions, the group S_A can be excluded from consideration.

The initial data taken for the SFD simulation (thousands of people) are as follows [40, 41, 42]:

$$S_B(0) = 249,\ L_A(0) = 8500,\ L_{Am} = 1150,\ L_B = 8656,\ L_{Bm} = 1189,$$
$$I(0) = 34,\ I_m(0) = 4,\ T(0) = 51,\ T_m(0) = 6.$$

The population increase $\Pi = 266$ (thousands of people), the total number of people in the population $N = 19439$ (thousands of people), the coefficient of mortality from all causes except for tuberculosis $\mu = 0,016$, and the coefficient of contagiousness $\beta = 0,025$. Also notice that the coefficients ρ and χ in the model are always in products. Therefore, we can introduce a new coefficient, $\tilde{\chi} = \rho * \chi$, and reconstruct it.

The parameters of simulation for the very fast "quenching" method are

$$T_{max} = 1,\ T_{min} = 10^{-50},\ c = m * \exp(-1/m),\ m = 7.$$

Not all parameters of the model need to be determined. We will determine only the parameters that directly affect the spread of the epidemic, $q = (\varepsilon, k, \nu, \delta, \delta_m, \tilde{\chi}, o)$. The initial vector of parameters, $q_{(0)} = (\varepsilon, k, \nu, \delta, \delta_m, \tilde{\chi}, o)^T \in \mathbb{R}^7$, is chosen arbitrarily. Since we know that all $q_{(0)_i} \in [1, 0]$ $(i = 1, \ldots, 7)$, we generate $q_{(0)_i}$ as a quantity uniformly distributed in the interval $[0, 1]$.

Since we plan to work with real data, assume that under the conditions of equations (1) for the model (8) the statistical data in the form of (9) are known only fort the number of uninfected people, S_B, being treated at times T, T_m. Therefore, taking (8), (9) as an exact solution of the inverse problem and the parameters from Table 3, we generate synthetic data for three functions of the model of (8) $(l_1 = 1, l_2 = 8, l_3 = 9)$: S_{B_k}, T_k, and T_{m_k}, measured once a year during four years. Subsequently these data are used as measurements to reconstruct the vector of parameters of the inverse problem for the model (8), (9).

Solving the inverse problem under the new conditions by the very fast simulated "quenching" method, we have obtained the following results. One can see in Fig. 6 (the objective functional of equation (10) versus the number of iterations) that the functional decreases with stochastic jumps. This conforms with the rules of constructing the method and its properties [33].

Let us introduce a concept of relative error $\frac{|q_j - q_{exact}|}{|q_{exact}|}$ and investigate its behavior. One can see in Fig 7 that the relative error decreases in a similar way.

Table 4 shows the results of reconstructing the vector of parameters $q \in \mathbb{R}^7$ from model measurements of three functions, namely, S_B, T, and T_m. One can see that not all of the parameters have been reconstructed with sufficient accuracy (see the last column of Table 4).

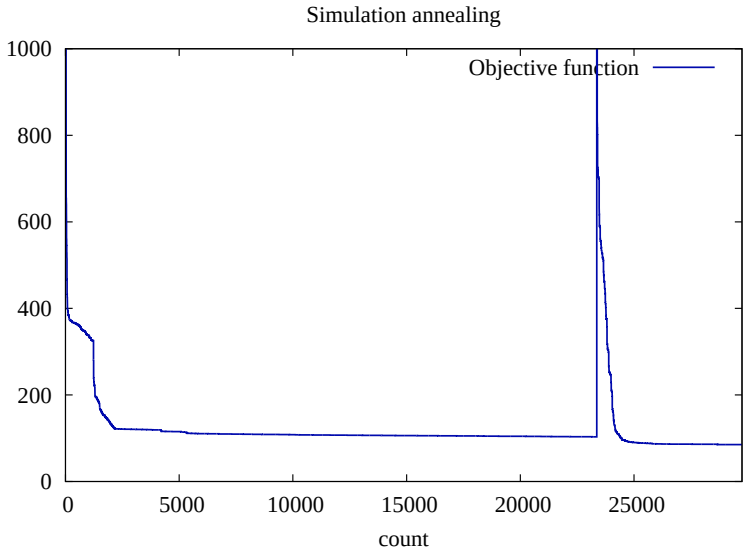

Figure 6: Objective function $J(q_j)$ versus the number of iterations j.

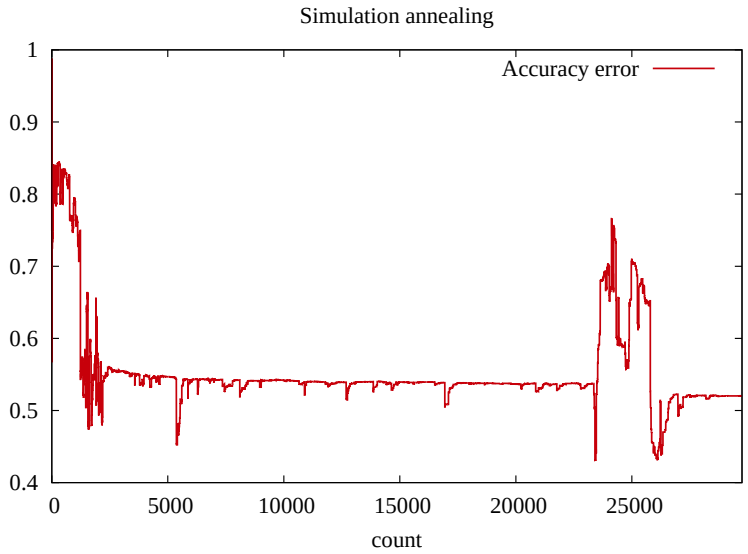

Figure 7: Relative error $\frac{|q_j - q_{exact}|}{|q_{exact}|}$ versus the number of iterations j.

Table 4: Numerical solution of the inverse problem for the model (8) with known measurements for the number of uninfected people and people under treatment.

Parameters		Combined method		
Symbol	Exact value	Initial approximation	Obtained solution	Common relative error
ε	0.129	0.186554	0.127367	
k	0.821	0.375305	0.8351	
ν	0.075	0.52066	0.0743568	
δ	0.72	0.943359	0.729983	0.3142
δ_m	0.035	0.617828	0.0352531	
$\tilde{\chi}$	0.343	0.709595	0.243029	
o	0.6	0.760315	0.996112	

Although not all of the parameters have been reconstructed with sufficient accuracy, the direct problem solution for the functions S_B, T, and T_m being measured has been reconstructed with good accuracy (see Fig. 8) taking into account that the measurements only for the first four years have been taken and the remaining 46 years have been used as the prediction.

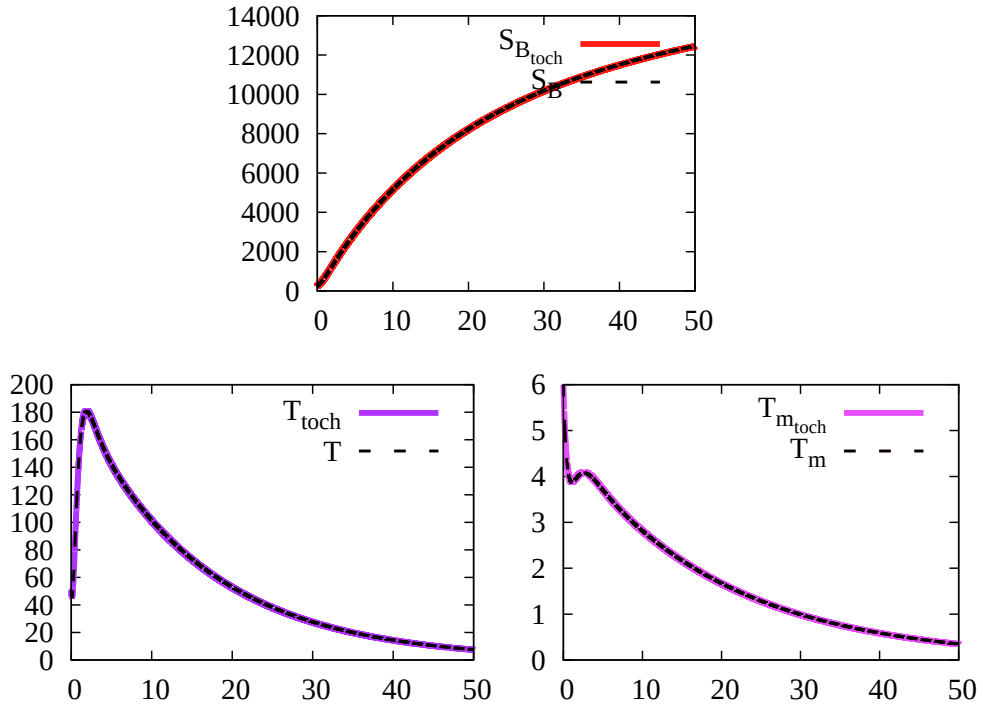

Figure 8: Number of uninfected people $S_B(t)$ and people under treatment for TB $T(t)$ and MDR-TB $T_m(t)$ (functions being measured) for the exact and reconstructed solutions for 50 years.

The other functions have been reconstructed with some errors. This can be explained by the insufficient accuracy of reconstruction of the parameters.

Note, that statistic data are known with some noise. Add to our four-years data (9) the Gaussian noise with level of 20%, zero expectation and root-mean-square deviation

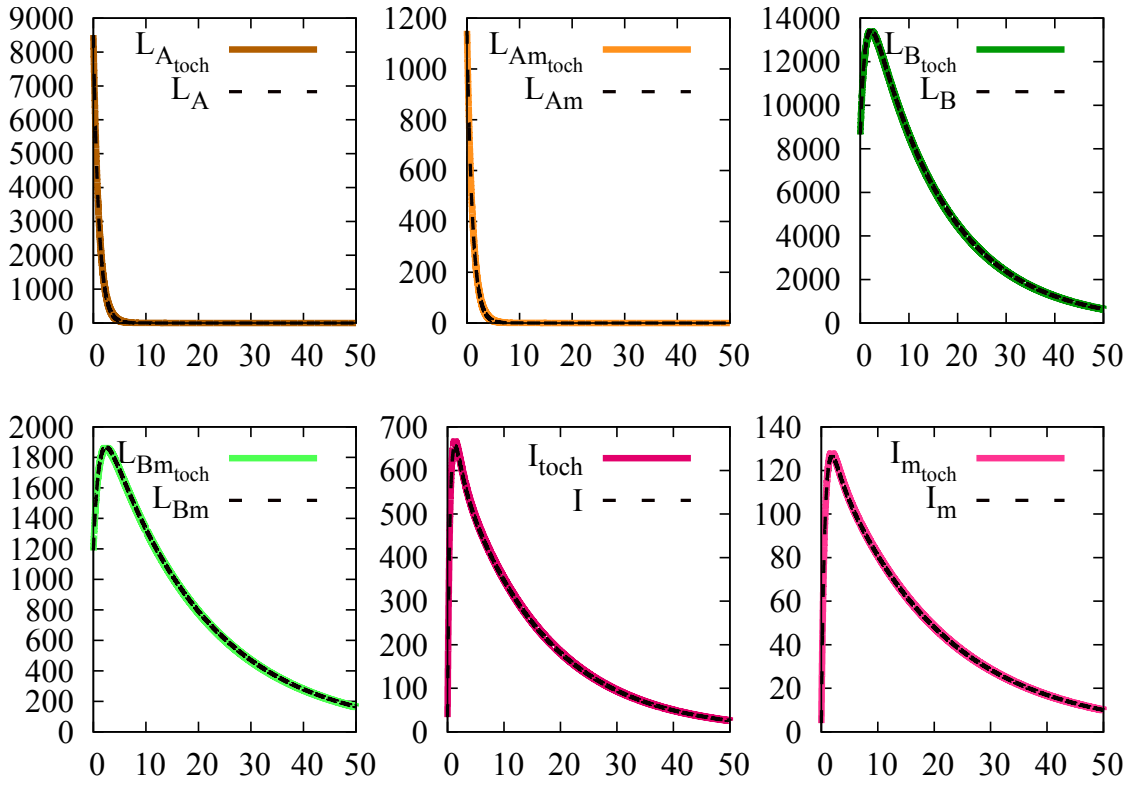

Figure 9: Number of latently infected people $L_A(t), L_{Am}(t), L_B(t), L_{Bm}(t)$ and people infected with TB $I(t)$ and MDR-TB $I_m(t)$ (functions not being measured) for the exact and reconstructed solutions for 50 years.

(is equal to 0.5 for S_{B_k}, to 0.2 for T_k and to 1.5 for T_{m_k}) and solve numerically inverse problem (8)-(9). The result of inverse problem solution for noisy data is presented in Table 5.

Table 5: Numerical solution of the inverse problem (8)-(9) with known 20% Gaussian noisy measurements for the number of uninfected people and people under treatment.

Parameters		Combined method		
Symbol	Exact value	Initial approximation	Obtained solution	Common relative error
ε	0.129	0.339386	0.101448	
k	0.821	0.332489	0.48391	
ν	0.075	0.640717	0.0609889	
δ	0.72	0.39212	0.908589	0.661907
δ_m	0.035	0.993866	0.04179941	
$\tilde{\chi}$	0.343	0.467896	0.824467	
o	0.6	0.166565	$1.2566 \cdot 10^{-5}$	

Note, that three reconstructed parameters k, $\tilde{\chi}$ and o are far from exact values. Parameter k appears in equations described the dynamic of latent infectious patients $L_A, L_{A_m}, L_B, L_{B_m}$. The additional information (9) for Tuberculosis inverse problem are known only for vaccinated S_B and infected patients under treatment T and T_m. For better accuracy for k it is necessary to obtain measurements about numbers of latent infectious patients in some previous years. The other two parameters $\tilde{\chi}$ and o include

in the second equation for $S_B(t)$, but due to stochastic error of 20% level in data for S_B of inverse problem the appropriate accuracy isn't reached. It happens because misfit function (10) not account errors in data. For the better parameters reconstruction for noisy data one should to use function depends on error level in data, for example, GLS method [43].

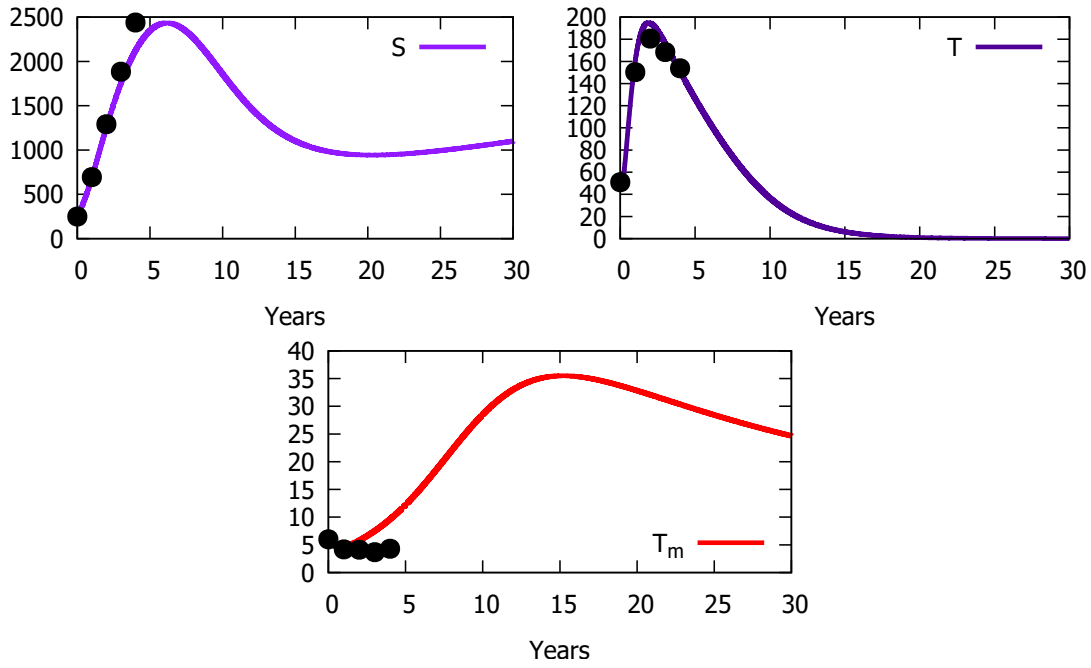

Figure 10: Number of uninfected people $S_B(t)$ and people under treatment for TB $T(t)$ and MDR-TB $T_m(t)$ (functions being measured) for the approximate reconstruction parameters after inverse problem solving with noisy data of level 20% for 30 years. The black dots are used noisy statistical information for the previous four years.

The common relative accuracy error for noisy data is sufficiently high but approximation of vaccinated (S_B) patients and patients with open form of the disease under treatment T, T_m is sufficiently good for the first four years and can be considered as the prediction with good accuracy (see Fig. 10).

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