Identifiability Analysis of Inverse Problems in Biology

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Abstract. The paper focuses on sensitivity-based identifiability analysis of parameters for mathematical models described by systems of nonlinear ordinary differential equations. This analysis is carried out using eigenvalue method and orthogonal method. Both methods allow one to globally evaluate and compare the influence of parameter values on measurement data. The sensitivity analysis and numerical experiments for mathematical model of the spread of TB and HIV co-infection are demonstrated. The numerical results show that 4 parameters (from 15 available) are identifiable uniquely by the given data only about 3 measured time-point functions during 5 years.

Introduction

Lately ordinary differential equations (ODEs) became the predominant tool in the field of biology (immunology, epidemiology), medicine (pharmacokinetics, tomography), sociology, economics, etc. Mathematical models are based on systems of ODEs (regular, nonlinear) and their coefficients characterize individual characteristics of patient and population in epidemiology field and should be identify for construction of individual treatment plan and the best forecasting of epidemic.

Before determining unknown parameters (inverse problem [1]), we should understand: whether there is a solution, how many parameters can we determine from the available data, how many measurements (additional information about solution of ODEs in fixed times) need to be taken to determine the required set of parameters. These questions are answered by analysis of the identifiability of mathematical model.

In this paper we investigate parameters of mathematical model of the spread of tuberculosis (TB) and HIV co-infection [2] by using two global methods of sensitivity-based identifiability analysis [3].

Problem Statement

We consider Cauchy problems of systems of ODEs in the vector form:

\[
\begin{cases}
    \dot{X}(t) = f(X(t), q), & t \in (0, T); \\
    X(0) = X_0,
\end{cases}
\]

where \( X(t) \) is vector of functions, \( q \) is vector of unknown parameters, \( X_0 \) is an initial condition.

The direct problem (1) with the initial conditions \( X_0 \) is solved by the Runge-Kutta method. Inverse problem consists in determining of parameter vector \( q \) using additional measurements at fixed time points \( t_k \):

\[
X_k(t_k; q) = y^k_i(q), \quad k = 1, \ldots, K, \ i = 1, \ldots, M,
\]
where \( M \) is a number of measured equations, \( K \) is a number of measurements.

Before solving inverse problem (1)-(2) we need to investigate the model on identifiability by using methods of sensitivity-based analysis.

**Orthogonal Method**

The orthogonal method builds a sequence of identifiable parameters based on investigation the (nearly) linear dependencies of columns of the sensitivity matrix [4]:

\[
S_{M-K\times L} = \frac{\partial y_j(t_k,q)}{\partial q_j} = \begin{bmatrix}
\frac{\partial y_1(t_1)}{\partial q_1} & \cdots & \frac{\partial y_1(t_K)}{\partial q_L} \\
\vdots & \ddots & \vdots \\
\frac{\partial y_j(t_1)}{\partial q_1} & \cdots & \frac{\partial y_j(t_K)}{\partial q_L} \\
\vdots & \ddots & \vdots \\
\frac{\partial y_M(t_1)}{\partial q_1} & \cdots & \frac{\partial y_M(t_K)}{\partial q_L}
\end{bmatrix}, \quad i = 1,\ldots,M, k = 1,\ldots,K, j = 1,\ldots,L.
\]

(3)

Thus, both the sensitivity of system response with respect to parameter values and the dependency between parameters regarding their effects on the system responses can be simultaneously evaluated to determine a set of identifiable parameters.

We use the following algorithm:

1) Set the stopping criterion \( \delta \), an array of identifiable parameters \( I = \emptyset \), and an array of non-identifiable parameters \( U = 1,\ldots,L \). Calculate the sensitivity matrix \( S \) (3).

2) Choose the column \( l \) with the largest sum of squares of the elements, add it to the matrix \( E \) as the first column, remove it from \( S \). Add the element \( l \) to the array \( I \) and delete it from \( U \).

3) If \( U \) is empty, then stop. All parameters are identifiable for this model. Otherwise, go to step 4.

4) For \( h = 1,\ldots,n \) (\( n \) is the number of remaining columns in \( S \)), compute the perpendiculars:

\[
S_n^+ = S_n - S_n^{\text{proj}} = \sum_{k=1}^{L} \left( S_k, E_k \right) E_k, \quad E = (E_1,\ldots,E_L).
\]

(4)

5) Choose the column \( l \) with the largest sum of squares of the elements. If \( \| S l \| \leq \delta \), then stop algorithm. All the parameters of \( I \) are identifiable. Otherwise, go to step 6.

6) Add the element \( l \) to \( I \), remove it from \( U \), the corresponding column remove from \( S \) and add to \( E \). Go to the step 3.

**Eigenvalue Method**

This approach finds unidentifiable parameters based on the properties of eigenvalues \( \lambda \) and eigenvectors \( u \) of the Hessian matrix \( H = S^T S \), where \( S \) is the sensitivity matrix (3).

We use the following algorithm:

1) Set the stopping criterion \( \delta \), an array of identifiable parameters \( I = 1,\ldots,L \), and an array of non-identifiable parameters \( U = \emptyset \). Calculate the sensitivity matrix \( S \) (3).

2) If \( I \) is empty, then stop. All parameters are non-identifiable for this model. Otherwise, step 3.

3) Calculate the Hessian matrix \( H = S^T S \), find eigenvalues \( \lambda^l (\lambda^1 \leq \ldots \leq \lambda^L \leq \ldots \leq \lambda^L) \) and eigenvectors \( u^l \) for it.

4) If \( \lambda^l \geq \delta \), then stop. The parameters in \( I \) are identifiable. Otherwise, step 5.

5) Choose \( l : ||u|| = \max \left( ||u^1||, ||u^2||, \ldots, ||u^L|| \right) \). Add \( l \) to the set of unidentifiable parameters \( U \), delete it from \( I \), delete the corresponding column from the matrix \( S \) and go to the step 2.
Mathematical Model

We consider the mathematical model of the spread of co-infection of TB and HIV with initial conditions, which is developed by a team of American researchers [2]:

\[
\begin{align*}
S &= \Lambda - \beta c S \left( I + J_1 \right) / N - \lambda \sigma S J^* / R - \mu S, \\
L &= \beta c (S + T) \left( I + J_3 \right) / N - \lambda \sigma L J^* / R - (\mu + k + r_3) L, \\
I &= k L - (\mu + d + r_2) I, \\
T &= r_1 L + r_2 I - \beta c T \left( I + J_3 \right) / N - \lambda \sigma T J^* / R - \mu T, \\
J_1 &= -\beta c J_1 \left( I + J_3 \right) / N + \lambda \sigma (S + T) J^* / R - (\alpha + \mu) J_1 + r^* J_2, \\
J_2 &= \beta c J_1 \left( I + J_3 \right) / N + \lambda \sigma L J^* / R - (\alpha + \mu + k^* + r^*) J_2, \\
J_3 &= k^* J_2 - (\alpha + \mu + d^*) J_3, \\
\bar{A} &= \alpha J_1 + \alpha J_2 + \alpha J_3 - (\mu + f) A, \\
S(0) &= S_0, L(0) = L_0, I(0) = I_0, T(0) = T_0, \\
J_1(0) &= J_{10}, J_2(0) = J_{20}, J_3(0) = J_{30}, A(0) = A_0.
\end{align*}
\]

Here \( N = S + L + I + T + J_1 + J_2 + J_3 + A, R = S + L + T + J_1 + J_2, J^* = J_1 + J_2 + J_3. \) Description of functions and parameters of the problem (5) are given in the Table 1.

Table 1. Definitions of parameters and state variables used in the model (5).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Units</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Lambda )</td>
<td>constant recruitment rate</td>
<td>Per year</td>
<td>Varied to population</td>
</tr>
<tr>
<td>( \beta c )</td>
<td>probability of TB infection per contact with a person with active TB</td>
<td>-</td>
<td>Varied to population</td>
</tr>
<tr>
<td>( \lambda \sigma )</td>
<td>probability of HIV infection per contact with a person with HIV</td>
<td>-</td>
<td>Varied to population</td>
</tr>
<tr>
<td>( \mu )</td>
<td>per-capita natural death rate</td>
<td>Per year</td>
<td>Varied to population</td>
</tr>
<tr>
<td>( k )</td>
<td>per-capita TB progression rate for individuals not infected with HIV</td>
<td>Year</td>
<td>0.05</td>
</tr>
<tr>
<td>( k^* )</td>
<td>per-capita TB progression rate for individuals infected also with HIV</td>
<td>Year</td>
<td>0.25</td>
</tr>
<tr>
<td>( d )</td>
<td>per-capita TB-induced death rate</td>
<td>Per year</td>
<td>0.1</td>
</tr>
<tr>
<td>( d^* )</td>
<td>per-capita HIV-induced death rate</td>
<td>Per year</td>
<td>0.2</td>
</tr>
<tr>
<td>( f )</td>
<td>per-capita AIDS-induced death rate</td>
<td>Per year</td>
<td>0.5</td>
</tr>
<tr>
<td>( r_1 )</td>
<td>per-capita latent TB treatment rate for individuals with no HIV</td>
<td>Per year</td>
<td>3</td>
</tr>
<tr>
<td>( r_2 )</td>
<td>per-capita active TB treatment rate for individuals with no HIV</td>
<td>Per year</td>
<td>1</td>
</tr>
<tr>
<td>( r^* )</td>
<td>per-capita latent TB treatment rate for individuals with also HIV</td>
<td>Per year</td>
<td>3</td>
</tr>
<tr>
<td>( \alpha_1 )</td>
<td>per-capita AIDS progression rate for individuals in J_1</td>
<td>Year</td>
<td>0.1</td>
</tr>
<tr>
<td>( \alpha_2 )</td>
<td>per-capita AIDS progression rate for individuals in J_2</td>
<td>Year</td>
<td>0.2</td>
</tr>
<tr>
<td>( \alpha_3 )</td>
<td>per-capita AIDS progression rate for individuals in J_3</td>
<td>Year</td>
<td>0.5</td>
</tr>
<tr>
<td>( S(t) )</td>
<td>number of susceptible individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( L(t) )</td>
<td>number of latent with TB individuals (without HIV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( I(t) )</td>
<td>number of infectious with TB individuals (without HIV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( T(t) )</td>
<td>number of successfully treated with TB individuals (without HIV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( J_1(t) )</td>
<td>number of HIV infectious individuals (without TB)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( J_2(t) )</td>
<td>number of HIV infectious and TB latent individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( J_3(t) )</td>
<td>number of infectious with both TB and HIV individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( A(t) )</td>
<td>number of full-blown AIDS individuals</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
For identifiability analysis of mathematical model (5) the additional information can be used at fixed time-points \( t_i \) just for three functions:

\[
I(t_k) = I_k, J_3(t_k) = J_{3k}, A(t_k) = A_k, \quad k = 1, \ldots, K.
\]  

We should find the set of parameters, which are identifiable for available measurements (6).

**Identifiability Analysis**

The TB and HIV co-infections model consists of 8 equations, but we can get measurements only from three of them (6) once a year during for 5 years \( M = 3, K = 5 \). Some of parameters of this model are determined from statistical information, we will check the mathematical model with respect to 6 parameters \( q = (k, k^*, r_2, \alpha_2, \alpha_3, \alpha_4)^T \). In this case we have the following sensitivity matrix:

\[
S_{M,K,S,L} = \frac{\partial y(t_k,q)}{\partial q_j} = \\
\begin{bmatrix}
L(t_1) & 0 & -I(t_1) & 0 & 0 & 0 \\
0 & J_2(t_1) & 0 & 0 & 0 & -J_3(t_1) \\
0 & 0 & J_1(t_1) & J_2(t_1) & J_3(t_1) & J_4(t_1) \\
\vdots & & \vdots & & \vdots & \\
L(t_K) & 0 & -I(t_K) & 0 & 0 & 0 \\
0 & J_2(t_K) & 0 & 0 & 0 & -J_3(t_K) \\
0 & 0 & 0 & J_1(t_K) & J_2(t_K) & J_3(t_K)
\end{bmatrix}
\]  

After using the identifiability methods we obtain the sequences of parameters from the most identifiable to the non-identifiable (Table 2).

<table>
<thead>
<tr>
<th>Parameter Set</th>
<th>Identifiability Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_1, k, \alpha_2, \alpha_3, k^*, r_2 )</td>
<td>Eigenvalue method</td>
</tr>
<tr>
<td>( \alpha_1, k, r_2, \alpha_3, k^*, \alpha_4 )</td>
<td>Orthogonal method</td>
</tr>
</tbody>
</table>

The Figure 1 shows us the logarithm of the value \( \delta \). There are the minimum eigenvalue for the eigenvalue method and the maximum perpendicular norm for the orthogonal method.

![Figure 1](image_url)

Figure 1. Logarithm of the value \( \delta \) for eigenvalue method (left) and for orthogonal method (right).

The larger the value \( \delta \), the less the number of identifiable parameters. For orthogonal method (Figure 1, right) all parameters except \( \alpha_2 \) are identifiable for \( \delta > 2.13 \). Parameters \( k^*, \alpha_4 \) are unidentifiable for \( \delta > 2.17 \). But, for the eigenvalue method (Figure 1, left) at once two parameters \( k^*, r_2 \) are unidentifiable for \( \delta > 0.583 \). We fix two parameters \( k^*, r_2 \) and analyze the model with

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respect of four unknown parameters \( q = (k, r_2, \alpha_1, \alpha_3)^T \). After using the identifiability methods we obtain the identifiable sequences of parameters (Table 3).

<table>
<thead>
<tr>
<th>Identifyability parameters</th>
<th>the value ( \delta )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_1 )</td>
<td>&gt;35320</td>
</tr>
<tr>
<td>( \alpha_1, k )</td>
<td>&gt;11</td>
</tr>
<tr>
<td>( \alpha_1, k, \alpha_2 )</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>( \alpha_1, k, \alpha_2, \alpha_3 )</td>
<td>&lt;2.3</td>
</tr>
</tbody>
</table>

We can see similar sequences and the same delta values for each method.

The results of the solution of the inverse problem (5)-(6) (determining of parameter vector \( q = (k, r_2, \alpha_1, \alpha_3)^T \)) by the very fast simulated re-annealing method [5] are presented in the Table 4.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative error in solution</th>
<th>( q )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha_1 )</td>
<td>1.0*10^{-6}</td>
<td>( q )</td>
</tr>
<tr>
<td>( \alpha_2 )</td>
<td>5.7*10^{-5}</td>
<td>( q )</td>
</tr>
<tr>
<td>( \alpha_3 )</td>
<td>5.3*10^{-6}</td>
<td>( q )</td>
</tr>
<tr>
<td>( k )</td>
<td>4.1*10^{-10}</td>
<td>( q )</td>
</tr>
</tbody>
</table>

It is seen that the relative error for each parameter is small (all four parameters recovered well), parameters \( \alpha, k \) recovered better than others, as shown by the identifiability analysis.

**Summary**

Two global methods of sensitivity-based identifiability analysis are described and demonstrated their application to the mathematical model of the spread of TB and HIV co-infection. It is shown that four parameters are identifiable uniquely by the given data only about numbers of infectious with TB individuals (without HIV), infectious with both TB and HIV individuals and full-blown AIDS individuals during at 5 years (once a year). In practice it is very important to investigate the model for identifiability before applying a numerical method for solving arising inverse problem.

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**References**


