IEEE Catalog Number: CFP1856H-PRT
ISBN: 978-1-5386-6467-4

KAZAKH KBTU BRITISH TECHNICAL UNIVERSITY

SDU

ADA UNIVERSITETI UNIVERSITY

12th IEEE International Conference

AICT 2018 INTERNATIONAL CONFERENCE

APPLICATION of INFORMATION and COMMUNICATION TECHNOLOGIES - AICT2018

Almaty, Kazakhstan
17-19 October 2018

CONFERENCE PROCEEDINGS

www.aict.info

Solving the Reverse Problems of Pharmacokinetics for a Linear Two-Compartment Model with Absorption

Baydaulet A. Urmashev, Aisulu T. Tursynbay, Almas N.Temirbekov, Aidana B. Amantayeva
Kazakh National University named after al-Farabi, Almaty, Kazakhstan
baydaulet.urmashev@kaznu.kz, tursynbay_a@mail.ru, almas.temirbekov@kaznu.kz, aman.aydana@gmail.com

Abstract — A new method is proposed for revealing the nonuniqueness of the solution of the inverse problem. The existence of three solutions of this equation is analytically proved and an algorithm for their finding is presented. The obtained results indicate the ambiguity of solutions of inverse problems and the obtained sets of parameters of the corresponding numerical methods for solving inverse problems of pharmacokinetics require additional conditions for determining the necessary set of pharmacokinetic parameters.

Keywords — Pharmacokinetics; nonuniqueness of the solution; inverse problems; numerical methods; linear two-compartment model with absorption;

I. INTRODUCTION

The theoretical proof of the nonuniqueness of the solution is confirmed by numerical calculations. To solve the inverse problem of models of pharmacokinetics, there were used several numerical methods that satisfy the criterion of the method of least squares. The software complex Pharmacokinetics 2.0 was developed. High performance will be provided by developing algorithms to solve the main problems in Fortran and C programming languages. These development programming languages are the fastest for implementation of complex mathematical calculations. The applications developed in these programming languages will be called through the architecture of micro services. Using the example of a computational experiment, the software complex was used for finding the pharmacokinetic parameters for a linear two-chamber pharmacokinetics model with absorption.

II. RELATED WORK

Previously, in the works [1, 2] we studied the kinetics of the reaction system (1), (2). It was shown that the equation of the dependence of concentration on time for component B has more than one solution. The result of this work is a rigorous analytical substantiation of the number of solutions of this equation and the identification of the conditions for the realization of each of them.

The chemical kinetics of processes (1-2) is described by the solution of the Cauchy problem for a system of linear ordinary differential equations (3-10):

$$\underset{C_1}{A} \xrightarrow{k_1} \underset{C_2}{B} \xrightarrow{k_2} \underset{C_3}{C} \quad (1)$$

$$\underset{C_2}{B} \xleftrightarrow{k_{3,4}} \underset{C_4}{D} \quad (2)$$

$$\frac{dC_1}{dt} = -k_1 C_1 \quad (3)$$

$$\frac{dC_2}{dt} = k_1 C_1 - (k_2 C_2 + k_3 C_2) + k_4 C_4 \quad (4)$$

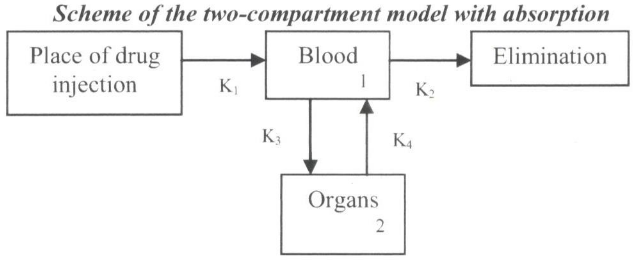
$$\frac{dC_3}{dt} = k_2 C_2 \quad (5)$$

$$\frac{dC_4}{dt} = k_3 C_2 - k_4 C_4 \quad (6)$$

$$C_1(0) = C_0, C_2(0) = 0, C_3(0) = 0, C_4(0) = 0, \quad (7\text{-}10)$$

here $C_i(t)$ - concentration of components **A, B, C, D** at the time moment t, k_i - rate constants of the individual reaction stages 1 and 2.

Scheme of the two-compartment model with absorption



On the basis of differential equations (3-6) with the above-mentioned initial conditions, the desired dependence $C_2(t) = f(t)$ - the dynamics of the change in the concentration of component **B** can be represented in the form of equation 11 [3, 4].

$$C_2(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} - A_3 e^{-k_1 t}, \quad (11)$$

where:

$$A_1 = \frac{k_1(\lambda_1 - k_4)\cdot C_0}{(\lambda_1 - \lambda_2)(k_1 - \lambda_1)} \quad (12)$$

$$A_2 = \frac{k_1(\lambda_2 - k_4)C_0}{(\lambda_1 - \lambda_2)(\lambda_2 - k_1)} \quad (13)$$

$$A_3 = -(A_1 + A_2) = \frac{k_1(k_4 - k_1)C_0}{(k_1 - \lambda_1)(k_1 - \lambda_2)} \quad (14)$$

$$\lambda_{1,2} = \frac{1}{2}\cdot\left[(k_2 + k_3 + k_4) \pm \sqrt{(k_2 + k_3 + k_4)^2 - 4k_2 k_4}\right] \quad (15)$$

$$\lambda_1 + \lambda_2 = k_2 + k_3 + k_4, \ \lambda_1\lambda_2 = k_2 k_4 \quad (16\text{-}17)$$

The solution of the direct problem in this case is not difficult. In Fig.1 presented calculated values of the concentration of substance **B** for the given values of reaction rate constants k_i and its initial concentration equal to 50.

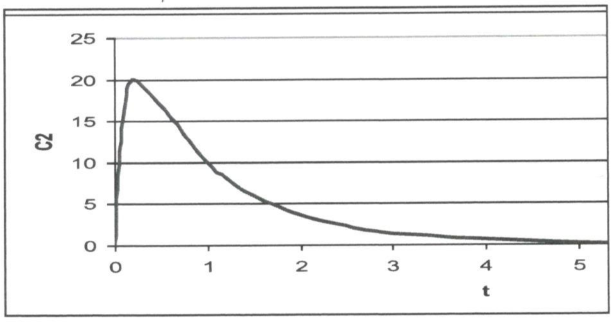


Fig. 1. Dependencies of concentration $C_2(t)$ on time for values.

$C_0 = 50, k_1 = 5, k_2 = 2, k_3 = 3, k_4 = 4$.

III. MATERIALS AND METHODS

The inverse problem is the calculation of the quantities k_i and C_0 on the basis of some set of measured values C_{2i} at the time moment t_i, in comparison to the straight one, is a much more complicated problem [4]. To solve it, equation (11) is presented in the following form (18):

$$C_2^{calc}(t) = L_1 e^{-\varepsilon_1 t} + L_2 e^{-\varepsilon_2 t} + L_3 e^{-\varepsilon_3 t} \quad (18)$$

Coefficients L_i and ε_i of this equation are related as follows:

$$L_1 + L_2 + L_3 = 0, \quad (19)$$

$$\varepsilon_1 \neq \varepsilon_2 \neq \varepsilon_3, \quad (20)$$

$$\varepsilon_1 > 0, \varepsilon_2 > 0, \varepsilon_3 > 0. \quad (21)$$

Taking into account equality (19), the total number of unknowns in equation (18) decreases until 5. Values of $L_1, L_2, \varepsilon_1, \varepsilon_2, \varepsilon_3$ were found by the method of least squares:

$$\sum_i \left(C_2^{\exp}(t_i) - C_2^{calc}(t_i)\right)^2 \to \min$$

where $C_2^{\exp}(t_i)$ - the concentrations found experimentally, $C_2^{calc}(t_i)$ - their calculated values.

After determining the values L_i and ε_i several options for assigning values $\varepsilon_1 \neq \varepsilon_2 \neq \varepsilon_3$ for $\lambda_1, \lambda_2, k_1$ were considered. Taking into account the conjugacy of the roots λ_1 and λ_2 ($\lambda_1 > \lambda_2$), and sampling two of three $\varepsilon_1, \varepsilon_2, \varepsilon_3$ possible, we can obtain the following cases:

$$1)\ \lambda_1 = \varepsilon_1,\ \lambda_2 = \varepsilon_2,\ k_1 = \varepsilon_3, \quad (22)$$

$$2)\ \lambda_1 = \varepsilon_2,\ \lambda_2 = \varepsilon_3,\ k_1 = \varepsilon_1, \quad (23)$$

$$3)\ \lambda_1 = \varepsilon_1,\ \lambda_2 = \varepsilon_3,\ k_1 = \varepsilon_2, \quad (24)$$

Further, using equations (12-14) to calculate the coefficients A_i, we obtain the systems of equations (12_1-14_1), (12_2-14_2) and (12_3-14_3) for calculating L_1^i, L_2^i, L_3^i, $i=\overline{1,3}$ respectively:

$$L_1^i = \frac{\varepsilon_3(\varepsilon_1 - k_4)\cdot C_0^1}{(\varepsilon_3 - \varepsilon_1)(\varepsilon_1 - \varepsilon_2)} \quad (12)$$

$$L_2^i = \frac{\varepsilon_3(k_4 - \varepsilon_2)\cdot C_0^1}{(\varepsilon_3 - \varepsilon_2)(\varepsilon_1 - \varepsilon_2)} \quad (13)$$

$$L_3^i = \frac{\varepsilon_3(\varepsilon_3 - k_4)\cdot C_0^1}{(\varepsilon_3 - \varepsilon_1)(\varepsilon_3 - \varepsilon_2)} \quad (14)$$

Since for constants L_i there are only values L_1, L_2, L_3 then the above systems of equations can be reduced to the following:

$$L_1^1 = L_3^2 = L_1^3 = L_1 \quad (25)$$

$$L_2^1 = L_1^2 = L_3^3 = L_2 \quad (25)$$

$$L_3^1 = L_2^2 = L_2^3 = L_3 \quad (25)$$

It follows that the initial concentrations for the three variants are related to each other by equality:

$$C_0^1 \varepsilon_3 = C_0^2 \varepsilon_1 = C_0^3 \varepsilon_2 \quad (26)$$

From the equation for calculating the rate constants k_4 (27), it is clear that in the realization of any of the three variants (22-24), its magnitude remains constant:

$$k_4 = -\frac{L_1\varepsilon_2\varepsilon_3 + L_2\varepsilon_1\varepsilon_3 + L_3\varepsilon_1\varepsilon_2}{L_1\varepsilon_1 + L_2\varepsilon_2 + L_3\varepsilon_3} \quad (27)$$

This leads to a very important conclusion in a practical sense: k_4 can serve as the main criterion for the selection of well-founded solutions describing the investigating set of points $C_2 - t$ for measured solution. To justify this conclusion, let us return to equations (16-17):

For $k_3 > 0$ we obtain the following inequality:

$$\lambda_1 + \lambda_2 > k_2 + k_4. \quad (28)$$

Then, from the equation (17) we can find k_2:

$$k_2 = \lambda_1 \lambda_2 / k_4 \quad (29)$$

and substituting it in (28), we obtain a new inequality of the form:

$$k_4^2 - (\lambda_1 + \lambda_2)k_4 + \lambda_1\lambda_2 < 0. \quad (30)$$

The solution of the last inequality can be represented in this form:

$$k_4 \in (\lambda_2, \lambda_1). \quad (31)$$

This means that the reaction rate constant (2) $k_3 > 0$ will be positive only if the computed value k_4 will be between the roots λ_1 and λ_2.

Otherwise, it will take a negative value. It should be noted that inequality (28) also holds in this case. For the computed values ε_i, connected by inequality (20), we find their maximum - $\varepsilon_{\max}$ and minimum - $\varepsilon_{\min}$ meanings. Now, one of the three values ε_i ($\bar{\varepsilon}$) belongs to the segment:

$$\bar{\varepsilon} \in (\varepsilon_{\min}, \varepsilon_{\max}).$$

From this it is not difficult to see that for k_4 two variants can be realized:

$$k_4 \in (\varepsilon_{\min}, \bar{\varepsilon}) \text{ and } k_4 \in (\bar{\varepsilon}, \varepsilon_{\max}).$$

Thus, the total number of solutions for equation (18) can be equal to three. Proof of the fact that the dependence $C_2(t) = f(t)$ can be simultaneously described by three sets of values k_i and C_0 S_n functions and Laplace transforms were used.

Originally, S_n denotes definite integrals, called the Laplace transforms:

$$S_n = C_0 \frac{k_1}{k_1 + n} \cdot \frac{n + k_4}{(\lambda_1 + n)(\lambda_2 + n)} \tag{32}$$

Here n - can be any real number, but for convenience there were taken integer values.

Since in the solution of the inverse problem for equation (11) or (18) it is necessary to determine the values of five unknowns, we can confine ourselves to five equations.

$$x_1 + nx_2 + \frac{1}{n^2}\left(1 - \frac{S_0}{S_n}\right)x_3 - \frac{S_0}{n \cdot S_n} x_4 = \frac{1}{n}\xi \tag{33}$$

where

$$x_1 = 1 + (\lambda_1 + \lambda_2)/k_1,\ x_2 = 1/k_1,\ x_3 = \lambda_1\lambda_2, \tag{34}$$

$$x_4 = k_{-2},\ \xi = -x_2 x_3 - (x_1 - 1)/x_2.$$

Then, by introducing new notation:

$$\begin{cases} ax_3 + bx_4 = \frac{1}{3}\xi \\ cx_3 + dx_4 = \frac{3}{4}\xi \end{cases} \tag{35}$$

And solving the system of equations (35) and taking into account that $x_i = B_i\xi$ we define successively all values B_i:

$$B_4 = \frac{\frac{1}{3}c - \frac{3}{4}a}{dc - ad},\ B_3 = \frac{\frac{1}{3}d - \frac{3}{4}b}{ad - bc} \tag{36-37}$$

$$B_2 = -\frac{1}{2} - \left(\frac{S_0}{S_1} - \frac{S_0}{4S_2} - \frac{3}{4}\right)B_3 - \left(\frac{S_0}{S_1} - \frac{S_0}{2S_2}\right)B_4 \tag{38}$$

$$B_1 = 1 - B_2 - \left(1 - \frac{S_0}{S_1}\right)B_3 + \frac{S_0}{S_1}B_4 \tag{39}$$

Further, substituting $x_i = B_i\xi$ into equation (34) we obtain the cubic equation (40)

$$B_2^2 B_3 \xi^3 + B_2\xi^2 + B_1\xi - 1 = 0, \tag{40}$$

The roots of which are found using the Cardano formula. The nonlinear equation (40) can be solved by a variety of different numerical methods, we chose the simplest of them - Newton's method. The algorithm for finding three values ξ_i is simple. First, using Newton's method, we determine the value ξ_1, and then using equality:

$$ax^3 + bx^2 + cx + d = (x - \xi)(ax^2 + (b + a\xi)x + a\xi^2 + b\xi + c) \tag{41}$$

and solving the quadratic equation:

$$ax^2 + (b + a\xi)x + a\xi^2 + b\xi + c = 0 \tag{42}$$

We find the remaining two solutions ξ_2 and ξ_3.

Thus, it follows from the above proof that for the measured solutions of $C_2(t)$ and the initial condition $C_2(0) = 0$, There are three sets of five permanent C_0, k_1, k_2, k_3, k_4 for the system (3-10).

1. For each of the variants of dependence $C_2(t) = f(t)$ with specified values of variables k_i and C_0 there are two more sets of these constants, that is, the inverse problem, in contrast to the straight one has three solutions.

2. Despite the fact that the given (measured) data set $C_2 - t$ can be described by three sets of constants k_i and C_0, only two of them have a physical meaning; The third set with a rate constant k_3, which has negative value and no physical meaning.

3. Thus, the inverse problem is the determination of the rate constants k_i and initial concentration C_0 by data $C_2 - t$ is incorrect, since the number of solutions is not equal to one [4]. And if the data set $C_2 - t$ is given by a direct problem, then the inverse problem, being ill-posed, has a stable solution. This is confirmed by the fact that one of the solutions found coincides with a given set of rate constants k_i and C_0.

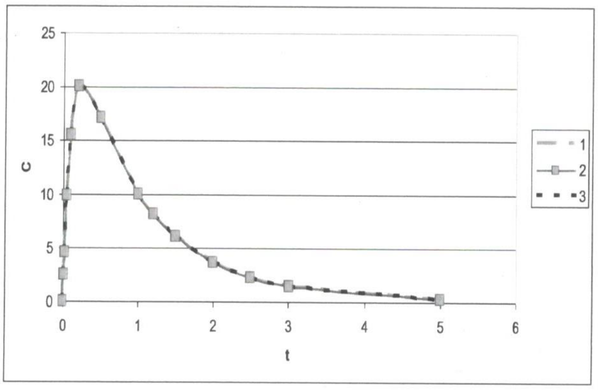


Fig. 2. Dependencies of $C_2(t)$ on time for different values $\xi_{1,2,3}$.

This fact also serves as a criterion for the correctness of the proposed mathematical apparatus and the calculations performed. In addition, the results of the study completely confirm the reliability of the data obtained earlier, where the proof of the non-uniqueness of the solution for the inverse problem was obtained in a different way [1, 2].

During the solution of inverse problem from experimental data, $C_2 - t$ is complicated by the fact that the instability is added to the problem of nonuniqueness of the solution. The problem of incorrectness of the inverse problem, caused by the instability of its solution, is one of the main problems in this field of knowledge. Its severity can be reduced by the continuous improvement of the optimization procedures used and the quality of the experiment. However, completely this problem can not be solved in principle.

IV. RESULTS AND DISCUSSION

To clarify the stability of finding the coefficients of the model of pharmacokinetics, experimental values of the dependence $C_2(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} - A_3 e^{-k_1 t}$ on time for values $C_0 = 50, k_1 = 10, k_2 = 1, k_3 = 5, k_4 = 3$. with a minimum absolute error in 1%.

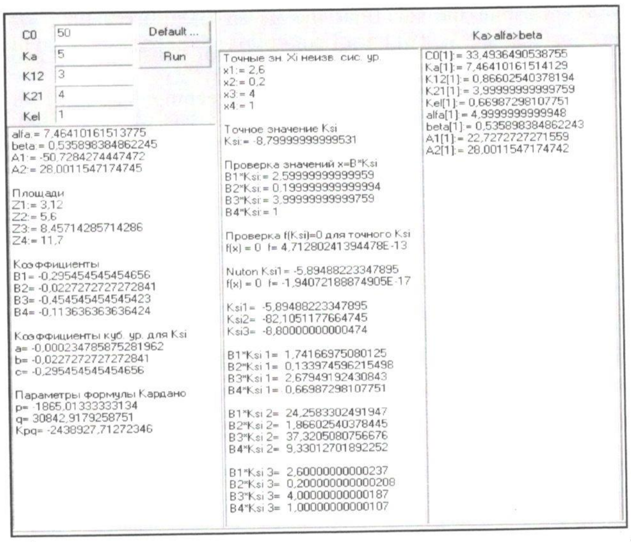


Fig. 3. Results of a numerical experiment, confirming the existence of three solutions for the equations (18) and respectively (11).

Using the proven methods of solving inverse problems, unknown parameters for the given experimental data were found. Unfortunately, the found parameters are very different from the model parameters. We can make sure to see the following figure.

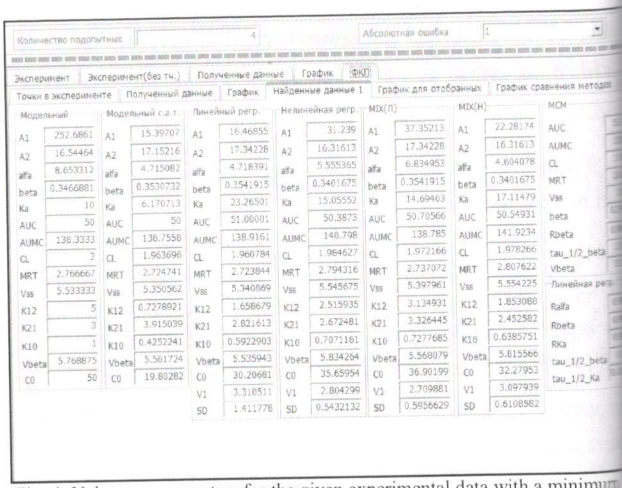


Fig. 4. Unknown parameters for the given experimental data with a minimum absolute error of 1%. were found .

You can also illustrate the graphical data for the parameters found using numerical methods.

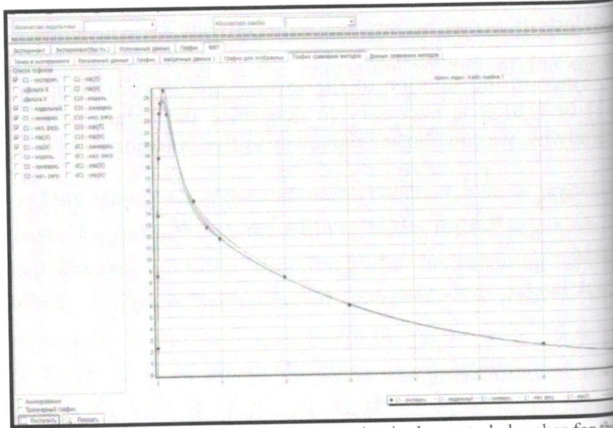


Fig. 5. Graphical dependences of concentration in the central chamber for the data from Fig. 4.

Here we can see a good 'coincidence for the central chamber of a linear two-chamber pharmacokinetics model with absorption. For the second chamber, the concentration curves are very different from the actual model concentration curve. This can be seen in the Fig. 6.

It can be seen from the figure that the concentration curves of the preparation in the peripheral chamber by quantitative values are almost two times different from the model preset values (red curve).

In the literature, there are many examples of the analysis of pharmacokinetic data [5-8]. A model is constructed for a particular process. Equations describing the corresponding model are given. There used the least squares method (LSM) for determining the parameters involved in the model equations, but often poorly or do not pay attention to the estimated statistical value.

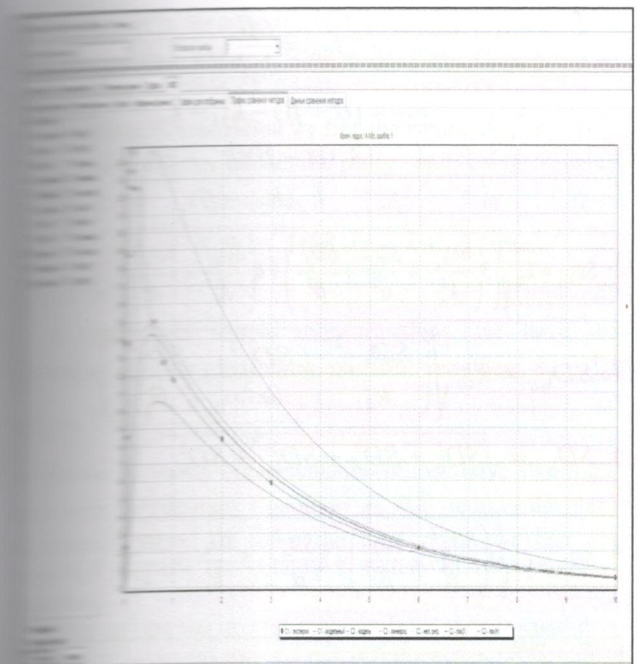


Fig. . Graphical dependencies of concentration in the peripheral chamber.

The purpose of this paper presents several important statistical aspects included in the describing equations and finding the values of the pharmacokinetic parameters with the corresponding confidence intervals. The general principle and procedure of the method is proposed in order to obtain statistical parameters.

A two-compartment model of pharmacokinetics with intramuscular injection is considered. The change in the concentration of drugs in the blood is described by the equation (54):

$$C(t_i) = A_1 e^{-\alpha t_i} + A_2 e^{-\beta t_i} - (A_1 + A_2) e^{-k_A t_i} \tag{43}$$

It is well known that the best statistical parameters can be determined using LSM. The present paper deals with the case of drug distribution, which are described by four parameters. When the experimentally found values $C_i^{\exp}$ characterizes by equation $C(t_i, A_1, A_2, \alpha, \beta, k_A)$,parameter $A_1, A_2, \alpha, \beta, k_A$ should give the minimum value of the weighted sum of squared differences between $C_i^{\exp}$ and $C(t_i, A_1, A_2, \alpha, \beta, k_A)$, that is,

$$S = \sum_{i=1}^{N} (C_i^{экс} - C(t_i, A_1, A_2, \alpha, \beta))^2 \cdot \omega_i \to \min \cdot \tag{44}$$

In our case ω_i =1, N is the number of experimental points. The S→min determines the values $A_1, A_2, \alpha, \beta, k_A$ in equation (54).

When $A_1^o, A_2^o, \alpha^o, \beta^o, k_A^o$ is the solution of inverse problem (54) for given experimental data $C_i^{\exp}$, then $A_1^o, A_2^o, \alpha^o, \beta^o, k_A^o$ accepted as approximate values $A_1, A_2, \alpha, \beta, k_A$ and respectively, the best parameters can be given in the following form

$$A_1 = A_1^0 + \Delta A_1 , A_2 = A_2^0 + \Delta A_2 , \alpha = \alpha^0 + \Delta\alpha,$$

$$\beta = \beta^0 + \Delta\beta, k_A = \Delta k^0 + \Delta k_A$$

where $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$ are growth for parameters $A_1, A_2, \alpha, \beta, k_A$, respectively.

The dependence $C(t_i, A_1, A_2, \alpha, \beta, k_A)$ is expanded in a Taylor series for $A_1^o, A_2^o, \alpha^o, \beta^o, k_A^o$. Then we determine that

$$\Delta C_i = C_i^{\exp} - C(t_i, A_1, A_2, \alpha, \beta, k_A).$$

Further, using the Taylor series expansion, we obtain the following equations:

$$\Delta C_i = \delta_o^i - \delta_{A_1}^i \Delta A_1 - \delta_{A_2}^i \Delta A_2 - \delta_\alpha^i \Delta\alpha - \delta_\beta^i \Delta\beta - \delta_{k_A}^i \Delta k_A$$

where

$$\delta_0^i = C_i^{\exp} - C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0),$$

$$\delta_{A_1}^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial A_1},$$

$$\delta_{A_2}^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial A_2},$$

$$\delta_\alpha^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial \alpha},$$

$$\delta_\beta^i = \frac{\partial C(t_i, A_1^0, A_2^0, \alpha^0, \beta^0)}{\partial \beta}.$$

Based on the LSM principle, the following system of equations is given for unknown quantities $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$.

$$\begin{cases} (\delta_{A_1},\delta_{A_1})\Delta A_1 + (\delta_{A_1},\delta_{A_2})\Delta A_2 + (\delta_{A_1},\delta_\alpha)\Delta\alpha + (\delta_{A_1},\delta_\beta)\Delta\beta + (\delta_{A_1},\delta_{k_A})\Delta k_A = (\delta_{A_1},\delta_0) \\ (\delta_{A_1},\delta_{A_2})\Delta A_1 + (\delta_{A_2},\delta_{A_2})\Delta A_2 + (\delta_\alpha,\delta_{A_2})\Delta\alpha + (\delta_\beta,\delta_{A_2})\Delta\beta + (\delta_{k_A},\delta_{A_2})\Delta k_A = (\delta_{A_2},\delta_0) \\ (\delta_{A_1},\delta_\alpha)\Delta A_1 + (\delta_{A_2},\delta_\alpha)\Delta A_2 + (\delta_\alpha,\delta_\alpha)\Delta\alpha + (\delta_\beta,\delta_\alpha)\Delta\beta + (\delta_{k_A},\delta_\alpha)\Delta k_A = (\delta_\alpha,\delta_0) \\ (\delta_{A_1},\delta_\beta)\Delta A_1 + (\delta_{A_2},\delta_\beta)\Delta A_2 + (\delta_\alpha,\delta_\beta)\Delta\alpha + (\delta_\beta,\delta_\beta)\Delta\beta + (\delta_{k_A},\delta_\beta)\Delta k_A = (\delta_\beta,\delta_0) \\ (\delta_{A_1},\delta_{k_A})\Delta A_1 + (\delta_{A_2},\delta_{k_A})\Delta A_2 + (\delta_\alpha,\delta_{k_A})\Delta\alpha + (\delta_\beta,\delta_{k_A})\Delta\beta + (\delta_{k_A},\delta_{k_A})\Delta k_A = (\delta_{k_A},\delta_0) \end{cases} \tag{45}$$

where

$$\delta_{A_1} = \{\delta_{A_1}^1, \delta_{A_1}^2, ..., \delta_{A_1}^N\}, \delta_{A_2} = \{\delta_{A_2}^1, \delta_{A_2}^2, ..., \delta_{A_2}^N\}, \delta_\alpha = \{\delta_\alpha^1, \delta_\alpha^2, ..., \delta_\alpha^N\},$$

$$\delta_\beta = \{\delta_\beta^1, \delta_\beta^2, ..., \delta_\beta^N\}, \delta_{k_A} = \{\delta_{k_A}^1, \delta_{k_A}^2, ..., \delta_{k_A}^N\},$$

$$\delta_{A_1}^i = e^{-\alpha^0 t_i} - e^{-k_A^0 t_i}, \delta_{A_2}^i = e^{-\beta^0 t_i} - e^{-k_A^0 t_i}, \delta_\alpha^i = -A_1^0 t_i e^{-\alpha^0 t_i}, \delta_\beta^i = -A_2^0 t_i e^{-\beta^0 t_i},$$

$$\delta_{k_A}^i = (A_1^0 + A_2^0) t_i e^{-k_A^0 t_i}.$$

The best parameters can be obtained by the roots of the above system (56). Solving the system of equations by the numerical method of Gauss determine the values of the unknowns $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$

The system (56) can be written in the following matrix form

$$\Lambda \cdot \Delta_x = \Delta_0$$

We denote by C the inverse matrix in (45)

$$C = \Lambda^{-1}$$

The solution $\Delta A_1, \Delta A_2, \Delta\alpha, \Delta\beta, \Delta k_A$ of system (45) can be represented in vector form:

$$\Delta_x = \Lambda^{-1} \cdot \Delta_0$$

here

$$\Lambda = \begin{pmatrix} (\delta_{A_1}, \delta_{A_1}) & (\delta_{A_1}, \delta_{A_2}) & \dots & (\delta_{A_1}, \delta_{k_A}) \\ (\delta_{A_1}, \delta_{A_2}) & (\delta_{A_2}, \delta_{A_2}) & \dots & (\delta_{k_A}, \delta_{A_2}) \\ \dots & \dots & \dots & \dots \\ (\delta_{A_1}, \delta_{k_A}) & (\delta_{A_2}, \delta_{k_A}) & \dots & (\delta_{k_A}, \delta_{k_A}) \end{pmatrix}$$

$$\Delta_0 = \left((\delta_{A_1}, \delta_o), (\delta_{A_2}, \delta_o), (\delta_\alpha, \delta_o), (\delta_\beta, \delta_o), (\delta_{k_A}, \delta_o)\right)$$

$$\Delta_x = (\Delta A_1 \; \Delta A_2 \; \Delta\alpha \; \Delta\beta \; \Delta k_A)^T$$

The statistical values are given by the following equations.

$$S = (\delta_0, \delta_0) - (\delta_{A_1}, \delta_0)\Delta A_1 - (\delta_{A_2}, \delta_0)\Delta A_2 - (\delta_\alpha, \delta_0)\Delta\alpha - (\delta_\beta, \delta_0)\Delta\beta - (\delta_{k_A}, \delta_0)\Delta$$

$\sigma^2 = S/(N-2)$ - sum of squares.

The standard deviation of the parameters of equation (43) $A_1, A_2, \alpha, \beta, k_A$:

$$SD_{A_1} = \sqrt{c_{11}\sigma^2}, SD_\alpha = \sqrt{c_{33}\sigma^2}, SD_\beta = \sqrt{c_{44}\sigma^2},$$

$$SD_{k_A} = \sqrt{c_{55}\sigma^2}.$$

where c_{ii} – elements of the inverse matrix of system of equations (56).

The covariance coefficient can be expressed as the percentage of the coefficient of change $\%CV = \dfrac{SD}{\theta_i} \times 100$

Where θ_i is one of the parameters $A_1, A_2, \alpha, \beta, k_A$.

Confidence intervals at 95% for each parameter can be given by the following equation:

$CI = SD \times t_{95}$.

By knowing the values $SD_{A_1}, SD_{A_2}, SD_\alpha, SD_\beta, SD_{k_A}$ it needs to be determined $SD_{C_0}, SD_{k_{21}}, SD_{k_{12}}, SD_{k_{10}}$

Let's write the formulas for constants:

$$k_{21} = \frac{\alpha\beta(A_1 + A_2) - A_1 k_A \beta - A_2 k_A \alpha}{A_1\alpha + A_2\beta - (A_1 + A_2)k_A};$$

$$k_{10} = \frac{\alpha\beta}{k_{21}};$$

$$k_{12} = (\alpha + \beta) - k_{21} - k_{10};$$

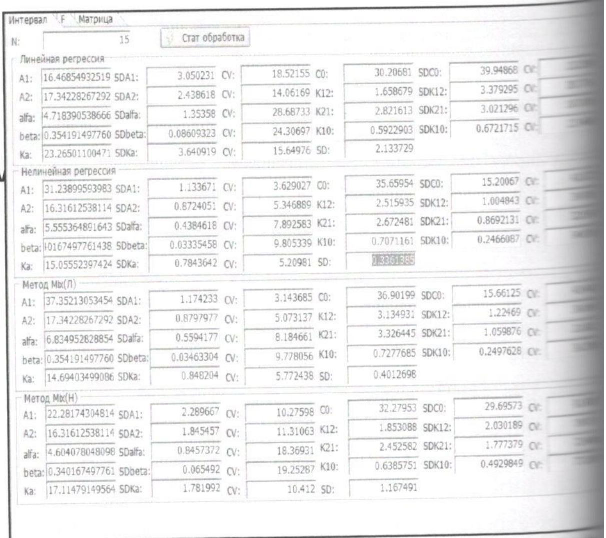
$$C_0 = \frac{A_2(\alpha - \beta)(k_A - \beta)}{k_A(k_{21} - \beta)};$$

1. $SD_{k_{21}} = k_{21}\sqrt{\left(3\left(\dfrac{SD_{k_A}}{k_A^2}^2 + \dfrac{SD_\alpha}{\alpha^2}^2 + \dfrac{SD_\beta}{\beta^2}^2\right) + 4\left(\dfrac{SD_{A_1}}{A_1^2}^2 + \dfrac{SD_{A_2}}{A_2^2}^2\right)\right)}$

2. $SD_{k_{10}} = k_{10}\sqrt{\left(\dfrac{SD_{k_{21}}}{k_{21}^2}^2 + \dfrac{SD_\alpha}{\alpha^2}^2 + \dfrac{SD_\beta}{\beta^2}^2\right)}$

3. $SD_{k_{12}} = \sqrt{SD_\alpha^2 + SD_\beta^2 + SD_{k_{21}}^2 + SD_{k_{10}}^2}$

4. $SD_{C_0} = C_0\sqrt{4\left(\dfrac{SD_{A_2}}{A_2^2}^2 + \dfrac{SD_\beta}{\beta^2}^2\right) + 2\dfrac{SD_\alpha}{\alpha^2}^2 + 5\dfrac{SD_{k_A}}{k_A^2}^2 + \dfrac{SD_{k_{21}}}{k_{21}^2}^2}$



Интервал | F | Матрица

N: 15 | Стат обработка

Линейная регрессия

A1:	16.46854932519	SDA1:	3.050231	CV:	18.52155	C0:	30.20681	SDC0:	39.94868
A2:	17.34228267292	SDA2:	2.438618	CV:	14.06169	K12:	1.658679	SDK12:	3.379295
alfa:	4.718390538666	SDalfa:	1.35358	CV:	28.68733	K21:	2.821613	SDK21:	3.021296
beta:	0.354191497760	SDbeta:	0.08609323	CV:	24.30697	K10:	0.5922903	SDK10:	0.6721715
Ka:	23.26501100471	SDKa:	3.640919	CV:	15.64976	SD:	2.133729		

Нелинейная регрессия

A1:	31.23899593983	SDA1:	1.133671	CV:	3.629027	C0:	35.65954	SDC0:	15.20067
A2:	16.31612538114	SDA2:	0.8724051	CV:	5.346889	K12:	2.515935	SDK12:	1.004843
alfa:	5.555364891643	SDalfa:	0.4384618	CV:	7.892583	K21:	2.672481	SDK21:	0.8692131
beta:	0167497761438	SDbeta:	0.03335458	CV:	9.805339	K10:	0.7071161	SDK10:	0.2466087
Ka:	15.05552397424	SDKa:	0.7843642	CV:	5.20981	SD:	0.3361385		

Метод Мь(Л)

A1:	37.35213053454	SDA1:	1.174233	CV:	3.143685	C0:	36.90199	SDC0:	15.66125
A2:	17.34228267292	SDA2:	0.8797977	CV:	5.073137	K12:	3.134931	SDK12:	1.22469
alfa:	6.834952828854	SDalfa:	0.5594177	CV:	8.184661	K21:	3.326445	SDK21:	1.059876
beta:	0.354191497760	SDbeta:	0.03463304	CV:	9.778056	K10:	0.7277685	SDK10:	0.2497628
Ka:	14.69403499086	SDKa:	0.848204	CV:	5.772438	SD:	0.4012698		

Метод Мь(Н)

A1:	22.28174304814	SDA1:	2.289667	CV:	10.27598	C0:	32.27953	SDC0:	29.69573
A2:	16.31612538114	SDA2:	1.845457	CV:	11.31063	K12:	1.853088	SDK12:	2.030189
alfa:	4.604078048098	SDalfa:	0.8457372	CV:	18.36931	K21:	2.452582	SDK21:	1.777379
beta:	0.340167497761	SDbeta:	0.065492	CV:	19.25287	K10:	0.6385751	SDK10:	0.4929849
Ka:	17.11479149564	SDKa:	1.781992	CV:	10.412	SD:	1.167491		

Fig. 7. Statistical data for the found pharmacokinetic parame several numerical methods.

An analytic proof of the existence of three solutions in solution of the inverse problem for equation (11) and representation of the algorithm for their finding are give this paper. The theoretical proof of the nonuniqueness solution is confirmed by numerical calculations [9-16].

In the numerical solution of (51) one can find one sol for equation (11). The remaining two solutions can determined with the help of the solution fo

V. CONCLUSION

After numerous numerical experiments in solving inverse problem for equation (11), finding some con through linearization is quite effective in terms of ite