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Numerical Solution of the Inverse Pharmacokinetic Problem for the Three- Compartment Model

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Abstract

This article considers the numerical solution of the inverse pharmacokinetics problem for a three-compartment linear model. First, the article presents some reviews of the pharmacokinetics problem and the three-compartment model. The following describes the formulation of the pharmacokinetics problem for a three-compartment linear model. The direct problem is the Cauchy problem for systems of ordinary differential equations. Solving the direct problem analytically, we find the concentration for the first compartment, since it is the object of the study. The formulation of the inverse problem is reduced to a nonlinear operator equation. For the inverse problem, seven coefficients concentration for the first compartment should be found for some additional information of a given concentration. The inverse problem is reduced to minimizing the objective functional. For the numerical solution, an adaptive search method is used genetic algorithm. The numerical results of this problem are given.

Keywords: inverse problems; three-compartment model; pharmacokinetics; ordinary differential equations; genetic algorithm.

1. Introduction

Pharmacokinetic models are widely used as a means of forecasting the disposition of drug in the body. This can be predicted by modeling the simultaneous distribution of drug through body tissue and clearance [1]. The fundamental pharmacokinetic concepts are volume and clearance. The time required to remove the drug from the body is determined by the ratio of volume to clearance [2]. Kinetics is defined as the rate of change of drug concentration expressed in units of concentration per unit of time. [3]. A compartment in the compartmental model is defined as a quantity of a substance which has uniform and perceptible kinetics of transformation and transport [4-6].

Pharmacokinetics studies on the way the body deals with absorption, distribution, metabolism, and excretion of drugs under investigation expressed in mathematical terms [7]. Applied pharmacokinetics is a challenging clinical discipline with a strong theoretical framework for impoving patient outcomes by controlling for variability in drug disposition among individuals [8].

Pharmacokinetic analysis is performed by non-compartmental (model independent) or compartmental methods. Compartmental pharmacokinetic analysis uses pharmacokinetic models to describe and predict the concentration-time curve. The main advantage of compartmental methods over non-compartmental methods is the ability to predict the concentration [7]. Multi-compartment modeling requires the adoption of several assumptions, such that systems in physical existence can be modeled mathematically:

1. Instant homogeneous distribution of materials within a compartment;
2. The exchange rate of materials among the compartments is proportional to the densities of these compartments. Such as the transfer rate from compartment i to compartment j is kijAi, while Ai is the mass of drug in compartment i and kij is a rate constant;
3. Usually, it is desirable that the materials do not undergo chemical reactions while transmitting among the compartments [9].

In practice the number of compartment is usually limited up to 3, since biological and assay variability do not permit estimation of additional coefficients and exponents from the observed data [10]. The poly-exponential disposition function can be mathematically transformed into a multi-compartment mammillary model with drug administration into a central compartment and transfer by first-order processes into peripheral compartments [11].

In 1968, Kruger-Thiemer first proposed a two-compartment model to achieve and maintain the steady state of blood drug concentration [8, 12]. The results demonstrated that a loading dose was necessary to fill up the initial volume of distribution in order to achieve steady state. In 1981, Schwilden proposed a method to maintain a constant drug concentration of central compartment (c1) in a three-compartment model [10].

2. Formulation of the problem

The differential equations describing the dynamics of changes in the number of drugs in the three-compartment

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linear model are calculated by the following formulas:

$$\frac{dm_a}{dt} = -k_a m_a \tag{1}$$

$$\frac{dm_1}{dt} = k_a m_a - \left(k_{12} + k_{el} + k_{13}\right) m_1 + k_{21} m_2 + k_{31} m_3 \tag{2}$$

$$\frac{dm_2}{dt} = k_{12} m_1 - k_{21} m_2 \tag{3}$$

$$\frac{dm_3}{dt} = k_{13} m_1 - k_{31} m_3 \tag{4}$$

$$\frac{dm_{el}}{dt} = k_{el} m_1 \tag{5}$$

initial conditions are added to the system of equations (1)-(5):

$$m_a(0) = m_0,\ m_1(0) = m_2(0) = m_3(0) = m_{el}(0) = 0 \tag{6}$$

Problems (1) - (6) describe the process of distribution of drug in the body. In this problem, the body is divided into three compartments. Compartment 1, the so-called central compartment, is a part of the body, at all points of which the concentration of the drug is $C_1(t)$. It consists of the heart and blood systems. Compartment 2 is the organs with high blood supply (kidneys, liver, lungs). The rest of the body belongs to Compartment 3 consisting of tissues with low blood supply (fat, bones, muscles, etc.) [13].

Let m_0 be the amount of the drug at the injection site, and m_1, m_2, m_3, m_{el} are its quantitative values in Compartments 1, 2, 3, respectively. V_1 a volume of blood. Then the concentration of the drug is calculated by the formula:

$C_a(t)=m_a/V_1$, $C_1(t)=m_1/V_1$, $C_2(t)=m_2/V_1$, $C_3(t)=m_3/V_1$, $C_{el}(t)=m_{el}/V_1$.

We consider the reaction system having the following scheme:

Then we divide equations of the system (1)-(6) and initial data by the corresponding volumes V_1, and we get a system of differential equations for concentrations $C_a(t, C_1(t), C_2(t), C_3(t), C_{el}(t)$:

$$\frac{dC_a}{dt} = -k_a C_a, \tag{7}$$

$$\frac{dC_1}{dt} = k_a C_a - \left(k_{12} + k_{13} + k_{el}\right) C_1 + k_{21} C_2 + k_{31} C_3, \tag{8}$$

$$\frac{dC_2}{dt} = k_{12} C_1 - k_{21} C_2, \tag{9}$$

$$\frac{dC_3}{dt} = k_{13} C_1 - k_{31} C_3, \tag{10}$$

$$\frac{dC_{el}}{dt} = k_{el} C_1, \tag{11}$$

with initial data:

$$C_a(0) = C_0,\ C_1(0) = C_2(0) = C_3(0) = C_{el}(0) = 0. \tag{12}$$

Solving the system (7)-(11) with the initial conditions (12), we find the function describing the concentration behavior in the central compartment:

$$C_1(t) = A_1 \cdot e^{-\alpha t} + A_1 \cdot e^{-\beta t} + A_1 \cdot e^{-\gamma t} - \left(A_1 + A_2 + A_3\right) \cdot e^{-k_a t}$$

here:

$$\alpha + \beta + \gamma = k_{12} + k_{21} + k_{13} + k_{31} + k_{el}, \tag{13}$$

$$\alpha\beta + \alpha\gamma + \beta\gamma = k_{12}k_{31} + k_{13}k_{21} + k_{21}k_{31} + k_{21}k_{el} + k_{31}k_{el} \tag{14}$$

$$\alpha\beta\gamma = k_{el}k_{21}k_{31}, \tag{15}$$

$$A_1 = \frac{k_a (k_{21} - \alpha)(k_{31} - \alpha)}{(k_a - \alpha)(\beta - \alpha)(\gamma - \alpha)} C_0, \tag{16}$$

$$A_2 = \frac{k_a (k_{21} - \beta)(k_{31} - \beta)}{(k_a - \beta)(\alpha - \beta)(\gamma - \beta)} C_0, \tag{17}$$

$$A_3 = \frac{k_a (k_{21} - \gamma)(k_{31} - \gamma)}{(k_a - \gamma)(\alpha - \gamma)(\beta - \gamma)} C_0, \tag{18}$$

In the direct problem (7)-(12) we find $C_1(t)$ on the following data $k_a, k_{12}, k_{21}, k_{13}, k_{31} k_{el}, C_0$. We find a function of the concentration in Compartment 1 via an analytical way:

$$C_1(t) = A_1 \cdot e^{-\alpha t} + A_1 \cdot e^{-\beta t} + A_1 \cdot e^{-\gamma t} - \left(A_1 + A_2 + A_3\right) \cdot e^{-k_a t} \tag{19}$$

To solve the direct problem the values of the parameters are k_a=1.5, k_{12}=1.0, k_{13}=1.0, k_{21}=0.15, k_{31}=0.1, k_{el}=0.1, C_0=5.0. We build a graphic of the function $C_1(t)$ on the segment [0;10] (fig. 1):

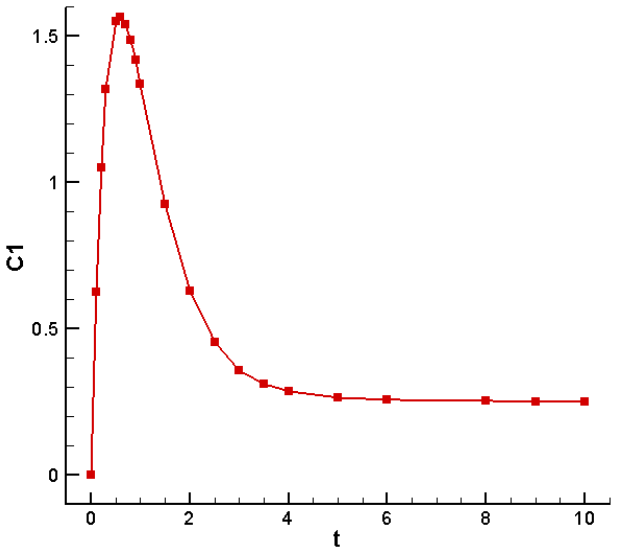

Fig 1. A graphic of the function $C_1(t)$

3. The inverse problem

Then we consider the values of the function $\left(C_1(t_1), C_1(t_2), \ldots, C_1(t_M)\right)$ in the set of points $(t_1, t_2, \ldots, t_M)$ and the operator associating a vector $q = \left(A_1, A_2, A_3 \alpha, \beta, \gamma, k_a\right)$ consisting of 7 components with a vector f, consisting of the values of the function $C_1(t)$ at the points $(t_1, t_2, \ldots, t_M)$, and denote it $A: R^7 \to R^M$. To

determine the seven unknown q values, we have a system of M nonlinear equations:

$$A(q) = f \tag{20}$$

$$q = \begin{pmatrix} A_1 \\ A_2 \\ A_3 \\ \alpha \\ \beta \\ \gamma \\ k_a \end{pmatrix}, \quad f = \begin{pmatrix} C_1(t_1) \\ C_1(t_2) \\ \vdots \\ C_1(t_M) \end{pmatrix}.$$

Operator A is nonlinear. Thus, we solve the inverse problem using the measured concentration data at M points, looking for the vector q, as a solution to the nonlinear equation (20) [14 - 16]. The solution to problem (20) is sought by minimizing the objective functional

$$J(q) = \sum_{j=0}^{M} \left(C_1(t_j) - f_j \right)^2 \tag{21}$$

4. The genetic algorithm

Genetic algorithms are adaptive search methods that have recently been used to solve optimization problems. They use both an analogue of the mechanism of genetic inheritance, and an analogue of natural selection.

Parent selection operators. Breeding states that only individuals whose fitness value is not less than a threshold value, for example, the average fitness value for a population can become parents. This approach provides faster convergence of the algorithm. However, due to the rapid convergence, the selective choice of the parent pair is not suitable when the task of determining several extremes is posed, since for such problems the algorithm, as a rule, quickly converges to one of the solutions. In addition, for some multidimensional problems with complex terrain of the objective function, fast convergence may turn into premature convergence to a quasi-optimal solution. This disadvantage can be partially compensated by the use of a suitable selection mechanism that would inhibit the too rapid convergence of the algorithm. The threshold value in the selection can be calculated in different ways. Therefore, in the literature on the genetic algorithm there are various variations of selection. The most famous of them are tournament and roulette (proportional) selections. In tournament selection, t individuals are randomly selected from a population containing N individuals, and the best of them are recorded in an intermediate array. This operation is repeated N times. Individuals in the resulting intermediate array are then used for crossing (also randomly). The size of the group of rows selected for a tournament is often equal to 2. In this case, they speak of a binary tournament. In general, t is called the number of the tournament. The advantage of this method is that it does not require additional calculations.

Recombination (reproduction). The recombination operator is applied immediately after the parent selection operator to obtain new progeny individuals. The meaning of recombination lies in the fact that the descendants created must inherit the gene information from both parents.

Intermediate recombination is applicable only to real variables, but not to binary ones. In this method, the numerical range of the gene values of the descendants is preliminarily determined, which should contain the gene values of the parents. Descendants are created according to the following rule.

Descendant = Parent 1 + α*(Parent 2 – Parent 1)

As the proponents of this method note, the most optimal reproduction is obtained when d = 0.25. For each gene of the descendant being created, a separate factor α is selected.

Mutation. After the reproduction process, mutations occur. This operator is necessary for "knocking out" a population from a local extremum and prevents premature convergence. This is achieved due to the fact that the randomly selected gene changes in the chromosome.

The operators of the selection of individuals in the new population. To create a new population, you can use various methods of selecting individuals.

Selection by repression. In this selection, the choice of a person in a new population depends not only on the size of its suitability, but also on whether there is already an individual in the population being formed with a similar chromosomal set. The selection is carried out from among the parents and their descendants. Of all the individuals with the same adaptability, preference is first given to individuals with different genotypes. Thus, two goals are achieved: first, the best-found solutions with different chromosome sets are not lost, and second, genetic diversity is constantly maintained in the population. Repression in this case forms a new population rather from distant individuals, instead of individuals grouped around the current found solution. This method is most suitable for multi-extremal problems, while in addition to defining global extremes, it is possible to single out those local extremes whose values are close to global ones [17].

5. Numerical calculations of the inverse problem

To test the operation of the algorithms, we give the exact solution $k_a = 1.5$, $k_{12} = 1.0$, $k_{13} = 1.0$, $k_{21} = 0.15$, $k_{31} = 0.1$, $k_{el} = 0.1$, $C_0 = 5.0$ according to which we define the value of the results of experiments $f = \left(C_1(t_1), C_1(t_2), \ldots, C_1(t_M) \right)$ where M = 21, t = {0.0, 0.1, 0.2, 0.3, 0.5, 0.6, 0.7.0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 9.0, 10.0}. With these values we will minimize the target functional.

Numerical results of the genetic algorithm:

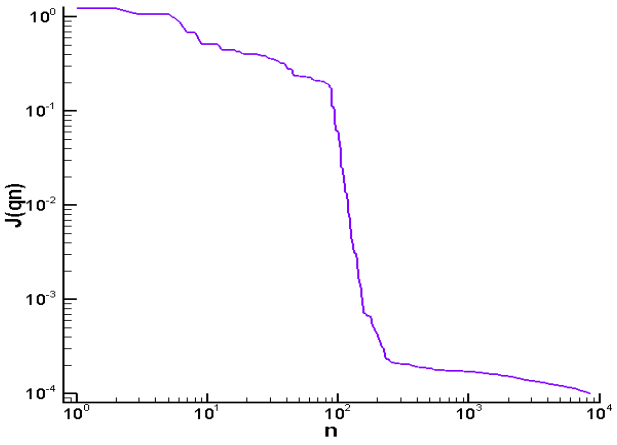

Fig 2. Graph of functional $J(q_n)$ and number iteration n=8538

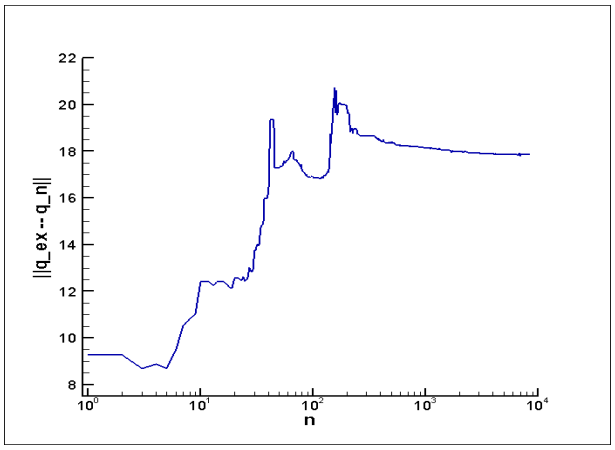

Fig 3. The norm of the difference between the exact value and the restored value $\|q_{exact} - q_n\|$.

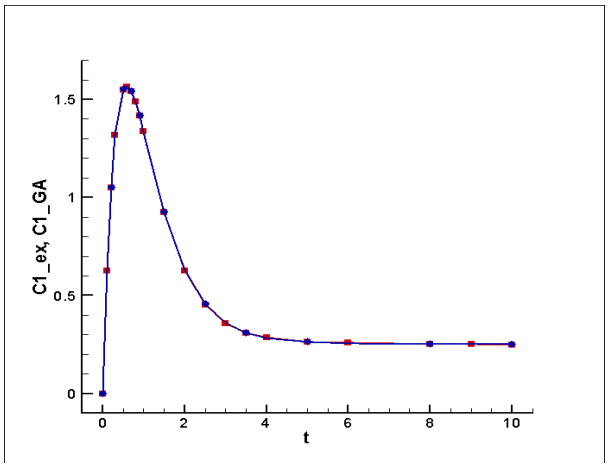

Fig 4. «Red»–■A precise solution, «Blue»–♦A solution by the method of GA

Table 1. Restored parameters of the system:

	A_1	A_2	A_3	α	β	γ	k_a
exact	-9.85	0.01	0.25	2.22	0.12	$5.4 \cdot 10^{-3}$	1.5
GA	5.74	-6.31	0.31	1.32	2.63	5.08	$1.3 \cdot 10^{-3}$

4. Conclusions

The numerical results of the inverse pharmacokinetic problem for the three-chamber model (figures 2-4, table 1) show that the concentration graph solved by the genetic algorithm coincides with the graph of exact data, and the coefficients are completely different, this leads to the fact that the solution is not the only one.

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