An Efficient Iteration Procedure for the Cluster Newton Method in Inverse Parameter Identification of Pharmacokinetics

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***Abstract*— In this paper, we proposed an efficient iteration procedure, being used in the initial cluster Newton method (CNM) to seek multiple solutions for inverse parameter identification in pharmacokinetics simultaneously. Instead of the constant level of perturbation in the initial CNM, the reasonable level of perturbation is controlled corresponding to different iterations. The simulation results of the proposed scheme have pointed out that we can reduce iterations and computational time; the point cluster goes more stably towards the solution manifold.**

***Keywords*— Pharmacokinetics (PK), Physiologically based pharmacokinetic (PBPK), Cluster Newton method (CNM), Lenvenberg-Marquardt method (LMM).**

I. INTRODUCTION

In pharmacokinetics, an underdetermined inverse problem (number of variables is greater than the number of equations) regularly appears, as the data which we collect does not often explain the complex mechanisms of the human body. Thanks to a mathematical model, complex activities can be simulated, and we can achieve worthy insight of pharmacokinetics in vivo. Lately, a new algorithm, the Cluster Newton method, has been developed by Aoki et al. [1] with the ability to find multiple solutions of an underdetermined inverse problem simultaneously. It has been proved that the Cluster Newton method has an advantage over the Levenberg-Marquardt method in terms of being reliable, robust, and efficient. Besides that, several approaches are proposed for improving the initial CNM as [2], [3], [4].

This paper proposes an efficient iteration procedure for the initial CNM to identify inverse parameters in pharmacokinetics. In the original CNM, after each iteration, the point cluster will move towards the manifold of solutions X^*. Creating randomly perturbed target values of y* is necessary to ensure the well-posedness of the least-squares problem (the current level of perturbation is 10%). After each iteration, the point cluster will go towards the solution manifold X^*, but the level of perturbation is not changed. Therefore, in this paper, after each iteration, when the point cluster is near to the manifold of solutions X^*, reducing the level of perturbation of y* is necessary, and it is suitable for a numerical stabilization. That is, we divided the Stage 1 into two Sub-stages (say Substage1 and Substage2). The Substage1 is solved by using a considerable level of perturbation of y* for the first few iterations, and the Substage2 is solved by using a small level of perturbation of y* for remaining iterations. Numerical results indicate that when using this approach, the point cluster moves more stably, we can also save the number of iterations and computation time.

II. PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK)

1. Forward problem: Pharmacokinetics model

First, the CPT-11 drug is dripped into the human body through intravenous. We use the PBPK model, which has been developed by Arikuma [5] to model concentrations of the CPT-11 drug, $u_1(t), \dots, u_{25}(t)$, and its metabolites (SN-38, SN-38G, NPC, and APC) in each part of the body (blood, adipose, GI, liver, and NET). Pathways connect each chemical compound in each part, $l_1, \dots, l_{55}$, which represent for inflow and outflow of chemical compounds. It is noted that the concentration change is due to the flow of chemical compounds; we can build a system of the first-order ODE of concentrations denoted by $u_i(t)$ as a function of time t.

Arikuma et al. have modeled the pathways, denoted $l_1, \dots, l_{55}$ in Figure 1. There are four kinds of pathways: i.v drip pathways, blood flow pathways, metabolic pathways, and excretion pathways. Each pathway offers a quantitative description of the flow rate of the drug with units of [nmol/min]. There are 60 parameters relating to these pathways; they are denoted as $x_1, \dots, x_{60}$ and their typical values are listed in Table B1-B5 in [5]. This inverse problem aims to estimate the parameters of this model better than the

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standard values listed in the table, based on data from clinical observations.

Since $u_1(t), \dots, u_{25}(t)$ are concentrations of CPT-11 and its metabolites in parts, with units of $\mu mol/L$. The concentration changes $\frac{du_i}{dt}$ are due to the inflow and outflow of the drug by pathways. Therefore, we can construct a system of ODE as below to model concentrations $u_i(t)$:

$$\frac{d}{dt}u = h(u, t; x) \quad (1)$$

It can be seen that this is a system of the first-order ODE, and we used the function "ODE15s" in Matlab to solve [7]. And then, we can obtain u(x_1, …, x_{60}; t) that depend on time t and parameters x_1, …, x_{60}. That is, $u_1(t), \dots, u_{25}(t)$ are can be estimated.

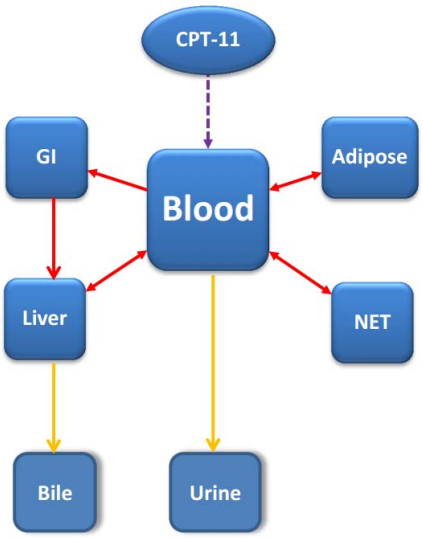

Figure 1. Simplified diagram of the PBPK model

2. Inverse problem: Model parameter identification

The inverse problem here means that we have the output data as an excretion profile in urine and bile ($y \in R^{10}$) and a model function of PBPK ($f: R^{60} \to R^{10}$), we need to estimate model parameters such as blood flow rate, the reaction speed of enzyme, tissue volume, and so on ($x \in R^{60}$). The model of the inverse problem is of the form:

$$y = f(x) \quad (2)$$

In the vector form, we have:

$$\begin{aligned}&[y_1, y_2, \dots, y_{10}]^T \\ &= [u_{26}(x_1, \dots, x_{60}; T), \dots, u_{35}(x_1, \dots, x_{60}; T)]^T \\ &= [f_1(x_1, \dots, x_{60}), \dots, f_{10}(x_1, \dots, x_{60})]^T\end{aligned} \quad (3)$$

The inverse problem might be classified as a problem of coefficient determination of the system of the ordinary differential equation. We use the ODE system to model the transportation and metabolism of anticancer drug CPT-11 and its metabolites. It is noted that, $u_1(t), \dots, u_{25}(t)$ depends on the parameters x_1, …, x_{60}, and now we obtain a mapping function from parameters (x_1, …, x_{60}) to the excretion profile ($y_1, y_2, \dots, y_{10}$). It means that using the PBPK model, we know the relationship between parameters in the human body (unknown parameters) and the output values (can be observed). By solving this inverse problem, we can find multiple feasible biological states of the patient consistent with the clinical observations.

3. Model problem description

The problem of parameter identification of the PBPK model is stated as following: Seek a set of points in $X \subset R^{60}$ close to a box X^0, satisfying:

$$y^* = f(x) \quad (4)$$

where

$f: X \subset R^{60} \to R^{10}$: a mapping function from model parameters to the excretion profile.

y^*: Clinical measurement data of the patient.

$X = \{x \in R^{60}: x_i > 0 \text{ và } \sum_{i=55}^{58} x_i < 1000\}$

$X^0 = \left\{x \in R^{60}: \max_{i=1,2,\dots,60} \left|\frac{x_i - \widehat{x_i}}{\widehat{x_i} v_i}\right| < 1\right\}$

The particular values of the PBPK's parameters are taken from Arikuma's work [5], and they are denoted as $\widehat{x_1}, \widehat{x_2}, \dots, \widehat{x_{60}}$. The variability of kinetic parameters are $\pm 50\%$ (i.e. $v_1 = \dots = v_{50} = 0.5$), physiological parameters are $\pm 30\%$ (i.e. $v_{51} = \dots = v_{58} = 0.3$) and i.v drip infusion parameters are $\pm 5\%$ (i.e. $v_{59} = v_{60} = 0.05$). The variability of the kinetic parameters were selected as a matter of fact that the variability between parts of the used values is smaller than ± 50% [9]. The variability of the physiological parameters is selected by [10]. The variability of i.v drip infusion parameters are chosen to be small because it is only affected by the accuracy of the drip infusion process.

III. Initial Cluster Newton Method (CNM)

As the proposed scheme is only utilized in Stage 1, the essential one, in the CNM. Hence, the CNM's Stage 1 is here presented as following:

1: Generate the initial points and object values.

1-1: Stochastically choose initial points $\left\{x_{.j}^{(0)}\right\}_{j=1}^{l}$ in the X^0 box. These points are saved in a $X^{(0)}$ matrix whose size is $60 \times l$, in which per column corresponds to a $x_{.j}$ point in R^{60}.

1-2: Create stochastically perturbed object values $\{y_j^*\}_{j=1}^{l}$ (to guarantee the well-posedness in Step 2-2) close to y*. Each value of $y_{.j}^*$ is chosen that satisfying:

$$\max_{i=1,2,\dots,10} \left|\frac{y_{ij}^* - y_i^*}{y_i^*}\right| < \eta \quad (5)$$

with $\eta = 0.1$, that is, the object accuracy in Stage 1 is $\pm 10\%$. These vectors are saved in a Y* matrix whose the j^{th} column corresponds to $y_{.j}^*$.

2: For k = 0, 1, 2, …, K_1

2-1: Resolve the forward problem corresponding to every point in $X^{(k)}$, that is:

$$Y^{(k)} = f\left(X^{(k)}\right). \quad (6)$$

2-2: Establish a linear approximation for f as follows:

$$f(x) \approx A^{(k)}x + y_0^{(k)} \quad (7)$$

It can be done by using a plane to fit for $Y^{(k)}$. We can find the slope matrix $A^{(k)}$ and the shift constant $y_0^{(k)}$ based on the least-squares solution of an over-determined linear equation system:

$$\min_{A^{(k)}\in R^{10\times 60},\, y_0^{(k)}\in R^{10}} \left\| Y^{(k)} - (A^{(k)}X^{(k)} + Y_0^{(k)}) \right\|_F \qquad (8)$$

where $Y_0^{(k)}$ is a matrix whose size is $10\times l$.

2-3: Seek the updated vector $s_{.j}^{(k)}$ of every column in $X^{(k)}$ based on a linear approximation which finds $s_{.j}$, satisfying:

$$y_{.j}^{*} = A^{(k)}\left(x_{.j}^{(k)} + s_{.j}^{(k)}\right) + y_0^{(k)} \qquad (9)$$

with $j = 1,2,\dots,l$.

It is the fact that matrix A is in the rectangular form that the number of columns is greater than the number of rows, leading an underdetermined linear equation system. Therefore, we cannot exclusively define $s_{.j}^{(k)}$ which gratifies Equation (9). Among all the solutions of Equation (9), we select the $s_{.j}^{(k)}$ vector that has the shortest scaled length as follows. The vectors $\left\{s_{.j}^{(k)}\right\}_{j=1}^{l}$ are shown as a matrix $S^{(k)}$ are the minimal norm solution of an underdetermined linear equation system:

$$\min_{S^{(k)}\in R^{60\times l}} \left\| diag(\hat{x})^{-1} S^{(k)} \right\|_F \text{ subject to } Y^{*} = (A^{(k)}(X^{(k)} + S^{(k)}) + Y_0^{(k)}) \qquad (10)$$

where $\hat{x} = (\widehat{x_1}, \widehat{x_2}, \dots, \widehat{x_{60}})$.

2-4: Seek new points which approximate the manifold of solutions X^{*} by using updated $X^{(k)}$. If needed, we lessen the vector length of $s_{.j}^{(k)}$ till the point $(x_{.j}^{(k)} + s_{.j}^{(k)})$ is in the f function's domain, that is:

For $j = 1,2,\dots,l$
  While $(x_{.j}^{(k)} + s_{.j}^{(k)}) \notin$ X
    $s_{.j}^{(k)} = \frac{1}{2} s_{.j}^{(k)}$
  End while
End for
$X^{(k+1)} = X^{(k)} + S^{(k)}$
End for

The relative error residual (RRE) is used to assess the algorithm accuracy of seeking multiple possible solutions, as follows:

$$r_j^{(k)}(x) = \max_{i=1,2,\dots,10} \left| \frac{y_{ij}^{(k)} - y_i^{*}}{y_i^{*}} \right| \text{ với } y_{.j}^{(k)} = f(x_{.j}^{(k)}). \qquad (11)$$

IV. An Efficient Iteration Procedure for the CNM

In this subsection, we proposed an efficient iteration procedure for CN approach to identify the inverse parameter in pharmacokinetics. It can be seen that, in the original CNM, after each iteration, the point cluster will move towards the solution manifold X^{*}. Creating randomly perturbed target values of y* is necessary to ensure the well-posedness of the least-squares problem (the current level of perturbation is 10%). After each iteration, the point cluster will go towards the solution manifold X^{*}, but the level of perturbation is not changed.

When the point cluster is far from the solution manifold X^{*}, the values of the elements in the point cluster is much different from those in the solution manifold. Therefore, we need to create a certain level of perturbation that is large enough to make a significant difference between the elements in the point cluster and in the solution manifold for ensuring the well-posedness of the least-squares problem.

When the point cluster is close to the solution manifold X^{*}, the values of the elements in the point cluster is not much different from those in the solution manifold. Therefore, we only need to create a smaller level of perturbation that also makes a significant difference between the elements in the point cluster and in the solution manifold for ensuring the well-posedness of the least-squares problem.

Therefore, after each iteration, when the point cluster comes next to the solution manifold X^{*}, reducing the level of perturbation of y* is necessary. It is suitable for a numerical stabilization. That is, we divided the Stage 1 into two Sub-stages. The Substage1 is solved by using a considerable level of perturbation of y* for the first few iterations, and the Substage2 is solved by using a small level of perturbation of y* for remaining iterations. Numerical results indicate that when using this method, the point cluster moves more stably, we can also save the number of iterations and computation time.

V. Simulation Results and Discussions

Simulation parameters: Sample number N_{samp}=500, Total iteration number N_{iter}=10, number of iterations of the first Substage $N_{1\text{-}iter}$=2, number of iterations of the second Substage $N_{1\text{-}iter}$=8, Accuracy of function evaluation $\delta_{ODE} = 10^{-3}$, level of perturbation for the first stage 10%, level of perturbation for the second stage 6%.

The RRE is presented in Table 1 using the initial CNM and the proposed scheme in N_{sum} iterations. In the first stage, the minimal RRE attaining by the algorithm is around 0.11, or 11%. Remarkably, it takes the initial CNM 7 iterations to achieve the minimal RRE; meanwhile, it just takes the proposed scheme five iterations. As a consequence, two iterations can be saved in this stage, and therefore, 1000 function estimations can be saved (since the initial CNM requests only a function estimation/point/iteration, here 500 points are used; thus, two iterations need 1000 function estimations). A large number of possible solutions need seeking, leading a significant amount of samples. Thence, it is essential to save iterations in the real system because it can decrease the substantial computational amount of the initial CNM.

Not just that, accompanied by the identical iteration number (ten iterations), the computing time of the proposed scheme is further considerably decreased, the computing time implemented by the proposed scheme is 417.2 seconds and by the initial CNM is 461.8 seconds, i.e., it is 9.67% reduced in computing time after ten iterations. In our simulations, the proposed scheme requires just five iterations (the initial CNM requires seven iterations), so the computing time by the proposed scheme reduces much more.

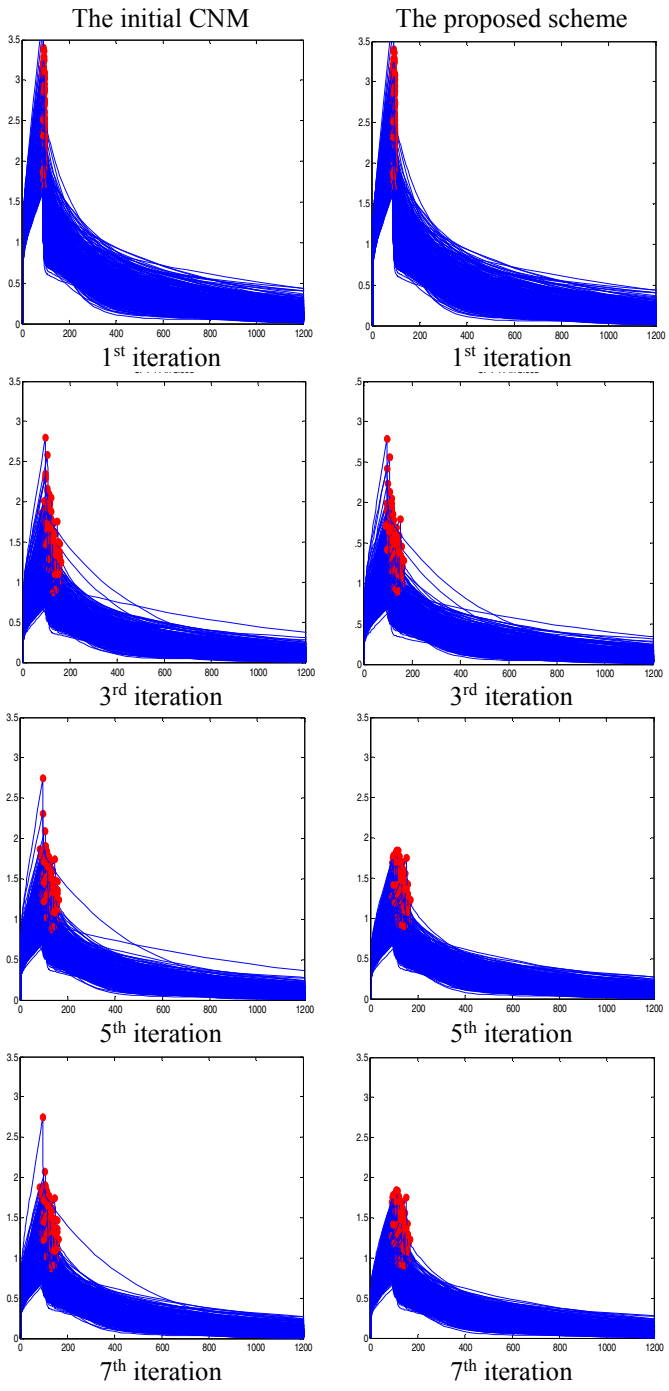

Figure 2. The CPT-11 concentration forecasted results in blood using 500 parameter sets, obtained by the initial CNM and proposed scheme

Figure 2 shows the CPT-11 concentration predicted results in blood, employing 500 sets of parameters, founded by the initial CNM and proposed scheme. By observation, it can be seen that, after the first three iterations, the difference between the initial CNM and proposed scheme is not shown clearly. Notwithstanding, after the iterators 5 and 7, we can see an obvious difference between the initial CNM and the proposed scheme. The point cluster in the proposed scheme goes more stably towards the manifold of solutions. In the meantime, in the initial CNM, several samples are still being dispersed far from the point cluster center.

VI. Conclusions

In this work, we have successfully carried out an efficient iterative approach to control the reasonable level of perturbation in the initial CNM to identify inverse parameters in pharmacokinetics. Consequently, using the proposed scheme, we can reduce iterations and computational time, and the point cluster goes more stably towards the solution manifold. With the achieved results, we can improve the proposed approach by investigating the optimal percent of perturbation generation of y*.

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Table 1. RRE of the original CNM and proposed scheme

Methods	RRE after each iteration (1-10)										Total time (sec)
The original CNM	3.1452	0.8131	0.5434	0.2516	0.1401	0.1324	0.1200	0.1155	0.1124	0.1115	461.882349
The proposed scheme	3.1452	0.8054	0.5270	0.1871	0.1268	0.1154	0.1111	0.1064	0.1049	0.1036	417.197260