PHAR 7633 Chapter 22

Non-Linear Regression Analysis of Pharmacokinetic Data
Individual Data and Population Analysis

Student Objectives for this Chapter

- Understand the use of computer programs such as Boomer for non-linear regression analysis of pharmacokinetic data
- Consider Bayesian analysis of clinical data
- Understand the use of computer programs such as NONMEM for non-linear regression analysis of population pharmacokinetic data

![Diagram Illustrating Data Analysis Paradigms](http://www.boomer.org/c/p4/c22/c22.html)

With no patient data but patient information no data analysis is required. Dosing calculation are based on nomograms, package inserts or other published information. If a few data points are available from a single patient and population parameter values for the drug of interest it may be possible to perform a Bayesian analysis. This analysis method can combine these two pieces of data. If only a few data points are available for each subject but data are available for many subjects a population analysis may be possible. This can also provide population parameter values with measures of the uncertainty in these values. More data in one subject allows 'traditional' non-linear regression analysis using graphical methods or a computer program. With more data from multiple subjects a population analysis is again very useful. Alternately a two step approach of analyzing each subject's data separately using non-linear regression analysis and combining these results may be applied.

This page (http://www.boomer.org/c/p4/c22/c2201.html) was last modified: Wednesday 26 May 2010 at 09:00 AM

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PHAR 7633 Chapter 22
Modeling of Pharmacokinetic Data

Why Model Data

Summarize Data

Pharmacokinetic models are very useful for summarizing data. A suitable model with good parameter value estimates and estimates of their uncertainty can be helpful. Thus, a model with population mean and standard deviation data could summarize pages and pages of data from many subject or patients.

During the development of new drugs and new dosage forms numerous pharmacokinetic studies in animals (pre-clinical) and humans (clinical) are performed. These and other studies will produce large amounts of data. Even a simple six subject study will provide considerable data. A full page of data.

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Subj #1 Wt 76 Kg Dose 200 mg Subj #2 Wt 74 Kg Dose 200 mg Subj #3 Wt 54 Kg Dose 150 mg

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Subj #4 Wt 58 Kg Dose 150 mg Subj #5 Wt 94 Kg Dose 250 mg Subj #6 Wt 82 Kg Dose 225 mg

Table 22.2.1 Data from six subjects

and numerous plots of the data.
Figure 22.2.1 Linear plot of concentration versus time data from subject 1

Figure 22.2.1 illustrates one of these plots of the data from just one subject. Also portrayed in Figure 6.2.1 is a simple one compartment model with two parameters, V and kel. If we model all the data in Table 6.2.1 we can summarize all these data with the model and averaged parameter values.

\[
\frac{dC_p}{dt} = -kel \cdot C_p
\]

\[
C_p = \frac{\text{Dose}}{V} \cdot e^{-kel \cdot t}
\]

\[
kel = 0.076 \pm 0.009 \text{hr}^{-1}
\]

\[
V = 10.7 \pm 2.3 \text{L}
\]

\[
V = 0.147 \pm 0.006 \text{L/kg}
\]

Table 22.2.2 Simple model and parameter values

Thus the data from six subjects can be summarized with an equation (model) and parameter values for the model.

Explore Mechanisms

Developing models is an important step in understanding how drugs are absorbed, distributed, metabolized or excreted. After developing good models it possible to explore correlations between pharmacokinetic parameter values and clinical parameters such as measures of renal, hepatic, cardiac or other patient characteristics. Developing and testing pharmacokinetic (and other models) is an important basis of scientific enquiry.

When we quantitate observations and model data we can better understand what is happening in the system under study. Correlation can be explored between the parameter values and other observations that may be collected. Table 6.3.1 provides pharmacokinetic parameters from a number of subject as well as some of the data that might be collected from a patient's hospital chart.
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Table 22.2.3 Pharmacokinetic parameters and patient data

With these data we could explore some of these correlations. For example plotting the kel measured in these patient versus the clinical parameter creatinine clearance may result in a plot such as Figure 22.2.2.

**Figure 22.2.2 Linear plot of observed kel versus creatinine clearance**

Figure 22.2.2 suggests that there is a significant correlation between elimination of this drug and renal function as expressed by the creatinine clearance. A large fraction of the drug dose must be excreted into urine. If renal function is poor elimination would be impaired and the drug dosage regimen should be adjusted appropriately. We could also explore the relationship between apparent volume of distribution and creatinine clearance.

**Figure 22.2.3 Linear plot of apparent volume of distribution and creatinine clearance**
In Figure 22.2.3 we see that there is little correlation between the apparent volume of distribution and creatinine clearance.

In another study we might look at the effect of drug dose and pharmacokinetic parameters. Some data are shown in Table 22.2.4.

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Table 22.2.4 Plasma concentrations after three different doses

Plotting these data on semi-log graph paper provides three lines with different slope and shape.

Figure 22.2.4 Semi-log plot of concentration versus time after three different doses

It would appear that these data represent nonlinear or saturable pharmacokinetics (which was discussed in more detail in Chapter 21). A model which could explain these data are shown in Figure 22.2.5 along with a plot of AUC versus dose. This is another representation of these and more data collected after additional dose values which illustrates the nonlinear model.
These and other mechanisms can be explored by modeling pharmacokinetic data.

**Make Predictions**

Once a satisfactory pharmacokinetic model and parameter values have been determined we can make predictions such as anticipated drug concentrations after a particular drug dosage regimen. Alternately we could calculate suitable dosage regimens to produce and maintain optimal drug concentrations.

Once we have a model and parameter values we can use this information to make predictions. For example we can determine the dose required to achieve a certain drug concentration.

**Dose required to achieve $C_p = 2 \text{ mg/L}$ at 6 hours after an IV dose.**

Given $k_{el} = 0.13 \text{ hr}^{-1}$ and $V = 15 \text{L}$

\[
C_p = \frac{\text{Dose}}{V} \cdot e^{-k_{el}t}
\]

\[
\text{Dose} = \frac{C_p \cdot V}{e^{-k_{el}t}}
\]

\[
= \frac{2 \times 15}{e^{-0.13 \times 6}} = 65 \text{mg}
\]

**Figure 22.2.6 Dose required to achieve a certain plasma concentration**

Using these data we can calculate (or predict) the drug concentrations at various time up to and including the six hours requested.
Figure 22.2.7 Plasma concentration versus time after a 65 mg IV bolus dose

We can also predict drug concentrations after a specified drug dosage regimen.
Calculate Cp after multiple IV doses

\[ Cp = \frac{Dose}{V} \cdot \left[ \frac{1 - e^{-n_{kel}t}}{1 - e^{-kel t}} \right] \cdot e^{-kel t} \]

Calculate Cp, 3 hours after four IV doses of 100 mg every 12 hours given \( kel = 0.23 \text{ hr}^{-1} \) and \( V = 14 \text{ L} \).

Figure 22.2.8 Concentrations after multiple IV Bolus doses

With this information we can predict drug plasma concentrations after multiple 100 mg IV bolus doses every 12 hours.

Figure 22.2.9 Linear plot of drug concentration versus time after multiple IV Bolus doses

With more extensive models even more involved predictions or calculations can be performed.

General Approach

Modeling involves a number of steps.

- Design Experiment
- Collect Data
- Develop Mathematical Model with ‘Parameters’
- Model Data
- Evaluate Fit to the Data
- Use Model

Figure 22.2.10 A general approach to modeling
Ideally the pharmacokinetic modeler is part of the design of the experiment. The study is designed and data are collected. The modeler will then develop suitable models consistent with the data, route of administration and dosage regimen. The data will be modeled using appropriate computer programs and the results evaluated. Problems at this point might lead to more modeling or even more studies and data collection. Finally we might get to use the model to make useful predictions such as dosage regimen design.

**Mathematical models as equations**

What is a mathematical model, a pharmacokinetic model? It can be useful to describe a model as a diagram with components to represent drug amount and arrows to represent rate processes. However, every pharmacokinetic model needs to be represented as a formula or an equation. Understanding these equations and the parameters in these equations is important.

As mentioned earlier, pharmacokinetic models are described as equations or formulas. In general there is a dependent variable (y variable) expressed as a function of independent variable(s) (x variable) with various constants and/or parameters.

\[ Y = f(x, p, c) \]

- y - dependent variable (observed, calculated data)
- x - independent variable (often time)
- p - parameters [adjustable] (e.g. kel, V)
- c - constants [fixed] (e.g. dose, duration)

**Figure 22.2.11 The dependent variable is a function of the independent variable(s) and ...**

Constants and parameters may be interchangeable or considered very similar. From a modeling point of view parameters are values that are determined by the computer program. Constants are terms that are held fixed during the modeling process.

Mathematical models take many forms. The simplest form is probably the equation for a straight line.

**Peak Height Ratio**

\[ \text{Peak Height Ratio} = \text{Slope} \times \text{Concentration} + \text{Intercept} \]

**Figure 22.2.12 Linear plot of y versus x for a straight line**
In Figure 22.2.12 peak height ratio is the dependent variable and concentration is the independent variable. Slope and intercept are parameters. This is an equation that is very useful for standard curves used in drug analysis.

A pharmacokinetic model is the next example. This is a very simple example which is not a straight line unless it is transformed. As an exponential equation there was usually two parameters, kel and V, with dose as the constant.
A third example is a pharmacological equation relating drug effect to drug concentration using a form of the Hill equation. The parameters in this model are $E_{\text{Max}}$, $EC_{50}$, and $\gamma$. We'll see more of this type of model in the next chapter.

$$\text{Effect} = \frac{E_{\text{Max}} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

Criteria of least squares

We need to decide on a criteria for a best fit when analyzing data and finding the best parameters values. If we put a line through data drawn on a piece of graph paper we can put the line where we think it looks best. However, if we want the computer program to find the best parameter values we need to have a well defined criteria. A commonly used criteria is the least squares criteria.
Least squares criteria refers to the formula used as a measure of how well the computer generated line fits the data. Thus it is a measure of the total of the differences between the observed data and the calculated data point. Most commonly with pharmacokinetic modeling these differences are measured in the vertical direction. That is, in the y axis values. Usually time is the x or independent variable and it should be possible to measure time accurately. The y axis or dependent variable, usually concentration, often involves an assay method which means there may be error (or variation) in each result.

Figure 22.2.15 Linear plot of Cp versus time illustrating error between observed data and calculated line

Again, usually the residual or error is assumed to be in the vertical direction although there are programs available that are capable of looking at oblique error in both the x and y direction. For the rest of our modeling discussion we will assume that the error is in the y axis variable only.

Looking at an individual data point and the calculated value with the same x value the residual can be expressed as a simple subtraction.

\[
\text{Residual} = Y_{\text{observed}} - Y_{\text{calculated}}
\]

**Equation 22.2.1 Residual in the y direction**

The problem is that overall the data points there might be high positive and high negative residuals that might cancel out. An absolute difference would solve this problem but squaring the residual is better statistically and achieves the same result.

\[
\text{Residual} = (Y_{\text{observed}} - Y_{\text{calculated}})^2
\]

**Equation 22.2.2 Residual in the y direction squared**

This gives us an equation of the residual for one data points. To complete the calculation we need to include the residuals for all the data points. This is called the sum of the squared residuals (SS).

\[
SS = \sum_{i=1}^{n} \left( Y_{\text{observed},i} - Y_{\text{calculated},i} \right)^2
\]

**Equation 22.2.3 Sum of the squared residuals**

Finally we need to take the error in each data point as a separate value. That is the error may be different for each measured, observed data point. We can compensate for this by applying a weight to each residual thus the usual criteria for a best fit is a minimum sum of the weighted, squared residuals (WSS).
\[ WSS = \sum_{i=1}^{n} \left( \frac{Y_{\text{observed},i} - Y_{\text{calculated},i}}{W_i} \right)^2 \]

Equation 22.2.4 Weighted sum of squared residuals

The job of the computer program is to produce a minimum value for WSS. This is also called the objective function. The fit with the minimum value of the WSS or objective function represents the best fit according to the least squares criteria. Inspection of Equation 22.2.4 leads to the conclusion that this can be achieved by changing the calculated values \((Y_{\text{calculated},i})\) by changing the parameter values. Other approaches such extended least squares, iterative reweighted least squares, Bayesian analysis and population analysis methods use modifications of this objective function.

Changing parameters to fit to the data

Once we have a suitable criteria we can have the computer program change the parameters value to achieve a best fit to the data. The computer program will systematically alter the each parameter until the least square criteria value is minimized. These systematic steps are called optimization algorithms. Some of these algorithms, such as the steepest descent, the Gauss-Newton and the Nelder-Mead methods are described elsewhere.

The data analysis computer program must change the parameter values to achieve a minimum value for the weighted sum of the squared residuals (WSS). This can be illustrated by changing the slope and intercept for the equation for a straight line. The calculated WSS changes with each change in the parameter values.

Another more involved example is the calculation of the best fit to data collected after oral administration. Two of the parameters involved in this model are \(k_a\) and \(k_e\). Adjusting the values of these parameters provide different values for the WSS.
Figure 22.2.17 Effect on WSS of adjusting kel and ka

You can download Excel spreadsheets (actually all in the same file) and try your own attempts at reducing the WSS. Change the parameter values and watch the value for the objective function, WSS, change. With a little ‘fiddling’ you should be able to get close to a best-fit. Try the straight line example first.
PHAR 7633 Chapter 22

Non-Linear Regression Analysis of Individual Subject Data

Analysis using a Non-linear Regression Program

In this section I will briefly describe how to set up one non-linear regression program, Boomer, which can be used in the analysis of pharmacokinetic data. Other programs used for non-linear regression analysis of pharmacokinetic data include SAAM II (Reference http://depts.washington.edu/saam2/), WinNonlin (Reference http://www.pharsight.com/products/prod_winnonlin_home.php) and ADAPT (Reference http://bmsr.usc.edu/Software/Adapt/adptmenu.html). Other useful pharmacokinetic programs are listed on this page.

Although graphical methods, such as we have used throughout this course, can be quite useful there are some significant limitations. A major limiting feature is that it must be possible to represent the data with a straight line. It may be possible to transform the data, for example by taking the log of the y value, but a straight line is still necessary. A problem with transforming the data is that the variance or error in each data point can be distorted inappropriately. It is fortunate that taking the log of the y-value (usually concentration) results in a reasonable representation of the variance. This is not generally the case as for example with ARE plots for urine data analysis.

Using non-linear regression analysis it is possible to assign a specific variance (or weight) to each data point that is appropriate the measurement. Thus data that are very accurately known can be analysed with data that are less accurately know by assigning a higher weight to the better data. Generally a weight equal to the reciprocal of the variance is applied to the data.

\[
\text{Weight} = \frac{1}{\text{Variance}}
\]

Equation 22.3.1 Ideally the Weight for each data point will be equal or proportional to the Variance of the Data Point

Another very useful feature of non-linear regression analysis is that we can fit more than one line simultaneously. For example we may give a drug to a subject and collect blood and urine samples at various times. The blood can be assayed for drug plasma concentration and the urine data can be assayed for drug concentration. These data, with appropriate weights, can be analyzed together to give a comprehensive fit to the data.
Figure 22.3.1 Plasma and Urine Data after IV Bolus Dose Administration

With non-linear regression analysis the shape of data curve doesn't matter. It can be a curve or straight line. There can be multiple lines (as above). The non-linear regression program simply adjusts the parameters of the model until the calculated line(s) best represents the data. Thus data collected during an IV infusion as well after the infusion has been stopped can be analyzed readily using non-linear regression analysis. Using graphical methods only the data after the infusion has finished could be analyzed.
Figure 22.3.2 Semi-log Plot of Cp versus time after a 2 hour IV Infusion

Program Set-Up - General approach

Model Visualization

The first step in the running a nonlinear regression problem is to visualize the model. The two factors which need to be considered are the route of drug administration and the data that has been collected. (Designing the experiment and planning the samples involves identifiability and optimal sampling, here we are concerned with modeling data already collected).

From the route of administration the modeler can include details in the model that describe the administration. This might be single or multiple dose regimens. Drug may be given by IV bolus injection, IV infusion, or an extravascular route such as oral, topical or inhalation. The extravascular routes may include multiple steps such dissolution and absorption in the case of oral administration or diffusion from a patch and through the skin in the case of a topical dose. The structure of this part of the model may be derived from an understanding of the dosage form and prior knowledge however certain parameter values may need to be determined by nonlinear regression. Dissolution rate constants, absorption rate constants or extent of absorption may be among the parameters to be estimated (example diagrams).

Consideration of the data plotted on linear and semi-log graph paper will provide more information about a suitable model. Distribution may be described with more than one compartment (example diagrams). More data types, such drug excreted in urine or metabolite concentrations, provide information useful in extending the model to better describe drug metabolism or excretion (example diagrams).

With some nonlinear programs it is possible to draw a sketch of a proposed models (SAAM II) or select a pre-drawn model from a library (WinNonlin). Users of other programs such as Boomer or ADAPT II may wish to draw this visualization by hand. Having a clear idea of what the model 'looks' like can be very useful in correctly defining the model with any nonlinear regression program.

Derive the Mathematical Model

A number of nonlinear regression program relieve the modeler from the chore of deriving the equations needed to describe the pharmacokinetic model. These programs include Boomer, SAAM II and WinNONLIN, although further model definition is possible if the equations are known. ADAPT II users and users of WinNONLIN with models that go beyond the built-in library will need to use equations to define the model. Differential equations can be derived directly from the model diagram. Integrated equation for most pharmacokinetic models can be derived using Laplace transforms. This method is discussed elsewhere in an introduction and more information.

Defining the Model within the Nonlinear Regression Program

Each program is somewhat different in the way one defines the model but there are three different approaches. Details of how models are define within any given program should be available within the program manual.

Selection from a library Some programs have a collection of predefined models within a library. The user simply selects the appropriate model from this library. WinNonlin is an example of this approach. It is probably the easiest for the user IF their model
is in the library. WinNonlin also allows the user to define more complicated models using a computer language. JGuiB allows the user to select a model for use with Boomer.

**Selection of Model Parameters** Programs like Boomer and SAAM II provide the user with a collection of parameters, rate constants, volumes, components (compartments), etc. (toolbox) from which the user can build their model. This provides the user with considerable flexibility without the need to derive the equations required for the model. SAAM II users have the added flexibility of modifying the form of some parameters. If the parameter toolbox is contains all the required parts this can be very convenient.

**Describe the Model within a Computer Program** For maximum flexibility the modeler can describe their model using a computer language. ADAPT II and WinNonlin (and to some extent SAAM II) are computer programs that provide this flexibility. Although this approach is flexible it does also require more of the modeler.

**Program Set-up - An Example using Boomer**

**Analysis Type**

METHOD OF ANALYSIS

0) Normal fitting  
1) Bayesian  
2) Simulation only  
3) Iterative Reweighted Least Squares  
4) Simulation with random error  
5) Grid Search

Non-linear regression analysis of a good number of data from one subject can be analyzed as a 'Normal Fitting'.

**Model Specification**

With Boomer the model is defined by selecting appropriate parameters from the types available.

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</tr>
<tr>
<td>1) Dose/initial amount</td>
<td></td>
</tr>
<tr>
<td>2) First order rate</td>
<td></td>
</tr>
<tr>
<td>3) Zero order</td>
<td>4-5) Vm and Km of Michaelis-Menten</td>
</tr>
<tr>
<td>6) Added constant</td>
<td>7) Kappa-Reciprocal volume</td>
</tr>
<tr>
<td>8-10) C = a * EXP(-b * (X-c))</td>
<td></td>
</tr>
<tr>
<td>11-13) Emax (Hill) Eq with Ec(50%) &amp; S term</td>
<td>14) Second order rate</td>
</tr>
<tr>
<td>15-17) Physiological Model Parameters (Q, V, and R)</td>
<td></td>
</tr>
<tr>
<td>18) Apparent volume of distribution</td>
<td>19) Dummy parameter for double dependence</td>
</tr>
<tr>
<td>20-22) C = a * SIN(2 * pi * (X - c)/b)</td>
<td></td>
</tr>
</tbody>
</table>

Special Functions for First-order Rate Constants

23-24) k = a * X + b  
25-27) k = a * EXP(-b * (X - c))  
28-30) k = a * SIN(2 * pi * (X - c)/b)  
31,32-33) dAt/dt = - k * V * Cf (Saturable Protein Binding)  
34-36) k * (1 - Imax * C/(IC(50%) + C)) Inhibition 0 or 1st order  
37-39) k * (1 + Smax * C/(SC(50%) + C)) Stimulation 0 or 1st order  
40) Uniform [-1 to 1] and 41) Normal [-3 to 3] Probability  
42) Switch parameter  
43) Clone component

Figure 22.3.3 Parameter types available with Boomer (Dec 2002)

For example, for a one compartment model with a 2 hour infusion used to analyze the data shown above in Figure 22.3.2, the model can be drawn as shown below, Figure 22.3.4
Figure 22.3.4 Diagram Illustrating a One Compartment Model with an IV Infusion

This model is described in the Boomer output in tabular format. Notice the use of parameters type 2 and 18 for kel and V, respectively. The infusion rate, a type 3 parameter, is turned off ('Stop'ped) at the value (2 hr) of the Duration, a type 0 parameter.

<table>
<thead>
<tr>
<th>Model and Parameter Definition</th>
<th>Name</th>
<th>Value</th>
<th>Type</th>
<th>From</th>
<th>To</th>
<th>Dep</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) kel</td>
<td>kel</td>
<td>= 0.9139E-01</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2) V</td>
<td>V</td>
<td>= 13.47</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3) Duration</td>
<td>Duration</td>
<td>= 2.000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4) k0</td>
<td>k0</td>
<td>= 100.0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 22.3.5 The Model Included in the Boomer Output

Data and Weight Specification

The x and y values (Time and Concentration) for each data set (line) are entered from the keyboard or from a data file already stored on the computer hard-drive. A weight can then be assigned by equation or independently entered by the user.

<table>
<thead>
<tr>
<th>Weighting function entry for [Drug]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0) Equal weights</td>
</tr>
<tr>
<td>1) Weight by 1/Cp(i)</td>
</tr>
<tr>
<td>2) Weight by 1/Cp(i)^2</td>
</tr>
<tr>
<td>3) Weight by 1/a*Cp(i)^b</td>
</tr>
<tr>
<td>4) Weight by 1/(a + b*Cp(i)^c)</td>
</tr>
<tr>
<td>5) Weight by 1/((a+b*Cp(i)^c)*d^(tn-ti))</td>
</tr>
</tbody>
</table>

Figure 22.3.6 Choices of Weight Equation provided in Boomer

More detail regarding these weight equations can be found in the Boomer manual or online.

Program Output

After successful completion of the Boomer run a detailed output file will provide information about the fit to the data using the model and selected weighting scheme. This output file will provide tabular, statistical and graphical output which can aid the analyst in the interpretation of the results.

Tabular and Statistical

(Section 1)

** FINAL OUTPUT FROM Boomer (v3.1.5) **

25 July 2005 --- 10:52:41 am
Title: Fit to data before and after termination of an IV infusion

Input: From Fig2202.BAT
Output: To Fig2202.OUT

Data for [Drug] came from keyboard (or ?.BAT)
Fitting algorithm: DAMPING-GAUSS/SIMPLEX
Weighting for [Drug] by 1/Cp(Obs)^2
Numerical integration method: 2) Fehlberg RKF45 with 1 de(s)
With relative error 0.1000E-03
With absolute error 0.1000E-03
DT = 0.1000E-02 PC = 0.1000E-04 Loops = 1
Damping = 1

(Section 2)

** FINAL PARAMETER VALUES ***

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Value</th>
<th>S.D.</th>
<th>C.V. %</th>
<th>Lower &lt;-Limit-&gt; Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>kel</td>
<td>0.91394E-1</td>
<td>0.431E-2</td>
<td>4.7</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>V</td>
<td>13.473</td>
<td>0.618</td>
<td>4.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Final WSS = 0.886379E-01 R^2 = 0.9671 Corr. Coeff. = 0.9834
AIC = -17.8088 Log likelihood = 8.02 Schwartz Criteria = -17.4143

R and R^2 - jp1 0.9856 0.9714
R and R^2 - jp2 0.9856 0.9714

(Section 3)

Model and Parameter Definition

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Value</th>
<th>Type</th>
<th>From</th>
<th>To</th>
<th>Dep</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>kel</td>
<td>0.9139E-01</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>V</td>
<td>13.47</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Duration</td>
<td>2.000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>k0</td>
<td>100.0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

(Section 4)

Data for [Drug] :-

<table>
<thead>
<tr>
<th>DATA #</th>
<th>Time</th>
<th>Observed</th>
<th>Calculated</th>
<th>(Weight)</th>
<th>Weighted residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.000</td>
<td>0.00000</td>
<td>0.00000</td>
<td>0.00000</td>
<td>0.00000</td>
</tr>
<tr>
<td>2</td>
<td>0.5000</td>
<td>3.80000</td>
<td>3.62770</td>
<td>0.263158</td>
<td>0.263158</td>
</tr>
<tr>
<td>3</td>
<td>1.000</td>
<td>7.40000</td>
<td>7.09336</td>
<td>0.135135</td>
<td>0.135135</td>
</tr>
<tr>
<td>4</td>
<td>1.500</td>
<td>10.8000</td>
<td>10.4042</td>
<td>0.0925926E-01</td>
<td>0.0925926E-01</td>
</tr>
<tr>
<td>5</td>
<td>2.000</td>
<td>0.00000</td>
<td>13.5672</td>
<td>0.00000</td>
<td>0.00000</td>
</tr>
<tr>
<td>6</td>
<td>3.000</td>
<td>12.0000</td>
<td>12.3822</td>
<td>0.083333E-01</td>
<td>0.083333E-01</td>
</tr>
<tr>
<td>7</td>
<td>5.000</td>
<td>9.00000</td>
<td>10.3137</td>
<td>0.011111</td>
<td>0.011111</td>
</tr>
<tr>
<td>8</td>
<td>9.000</td>
<td>8.00000</td>
<td>7.15558</td>
<td>0.012500</td>
<td>0.012500</td>
</tr>
<tr>
<td>9</td>
<td>12.00</td>
<td>5.00000</td>
<td>5.43962</td>
<td>0.020000</td>
<td>0.020000</td>
</tr>
<tr>
<td>10</td>
<td>18.00</td>
<td>3.90000</td>
<td>3.14352</td>
<td>0.0256410</td>
<td>0.0256410</td>
</tr>
<tr>
<td>11</td>
<td>24.00</td>
<td>1.70000</td>
<td>1.81662</td>
<td>0.0588235</td>
<td>0.0588235</td>
</tr>
</tbody>
</table>

WSS for data set 1 = 0.8864E-01
R^2 = 0.9671 Corr. Coeff. = 0.9834
R and R^2 - jp1 0.9856 0.9714
R and R^2 - jp2 0.9856 0.9714

Maximum value for [Drug] is 12.000 at 3.000

(Section 5)

Calculation of AUC and AUMC based on trapezoidal rule
### AUC and AUMC for [Drug] using Observed data

<table>
<thead>
<tr>
<th>Time</th>
<th>Concentration</th>
<th>AUC</th>
<th>AUMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00000</td>
<td>(0.00000)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50000</td>
<td>3.80000</td>
<td>0.95000</td>
<td>0.47500</td>
</tr>
<tr>
<td>1.00000</td>
<td>7.40000</td>
<td>3.75000</td>
<td>2.80000</td>
</tr>
<tr>
<td>1.50000</td>
<td>10.80000</td>
<td>8.30000</td>
<td>8.70000</td>
</tr>
<tr>
<td>2.00000</td>
<td>0.00000</td>
<td>11.0000</td>
<td>12.7500</td>
</tr>
<tr>
<td>3.00000</td>
<td>12.0000</td>
<td>17.0000</td>
<td>30.7500</td>
</tr>
<tr>
<td>5.00000</td>
<td>9.00000</td>
<td>38.0000</td>
<td>111.750</td>
</tr>
<tr>
<td>9.00000</td>
<td>8.00000</td>
<td>72.0000</td>
<td>345.750</td>
</tr>
<tr>
<td>12.0000</td>
<td>5.00000</td>
<td>91.5000</td>
<td>543.750</td>
</tr>
<tr>
<td>18.0000</td>
<td>3.90000</td>
<td>118.200</td>
<td>934.350</td>
</tr>
<tr>
<td>24.0000</td>
<td>1.70000</td>
<td>135.000</td>
<td>1267.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>153.601</td>
<td>1917.29</td>
</tr>
</tbody>
</table>

**Secondary Parameters**

MRT = 12.482

Half-life values for each first order rate constant

Parameter 1 has a half-life of kel is 7.58

Dose/AUC (= Clearance/F)

Parameter 4 gives k0/AUC (CL/F) of -0.651

---

**Figure 22.3.7 Tabular and Statistical Output provided by Boomer**

(Section 1) Preliminary Output describing the input/output details, the fitting (optimization) algorithm, integration method and weighting scheme.

(Section 2) Best-fit parameter values with statistical information are provided. The parameter CV values, the WSS, AIC and other values provide information about the model and how well the data have been fit to the model.

(Section 3) The model definition section provides the opportunity to confirm that the model has been described correctly.

(Section 4) The data are provided next as observed x and y values, calculated y values and weight and residual information. The observed data in this table should be checked against the correct values. Systematic differences between observed and calculated values may be detected in this section if the data analysis is incorrect.

(Section 5) The program can calculate the AUC and a number of 'secondary' parameters including MRT, half-life, and Dose/AUC. A zero time point must be entered for accurate estimates of AUC.
Graphical

(Section 1)
Plots of observed (*) and calculated values (+) versus time for [Drug]. Superimposed points (X).

13.57 Linear

13.57 Semi-log

(Section 2)
Plot of Std Wtd Residuals (X)
Figure 22.3.8 Graphical Output provided by Boomer

(Section 1) A linear and semi-log printer-type plot of the observed and calculated y-values versus the x-values. Systematic deviations, indicating a poor weighting scheme or model selection, may be apparent from these graphs.

(Section 2) Standardized weighted residuals versus x-value or log(calculated y value) are very useful tools for detecting poor model or weighting scheme selection. Any obvious pattern in these plots should be explored as potential evidence of a poor fit to the data.

The Boomer control file used in this analysis is provided here and the complete output file is provided here.

Other PK software is listed on http://www.boomer.org/pkin/soft.html

This page (http://www.boomer.org/c/p4/c22/c2203.html) was last modified: Wednesday 23 Feb 2011 at 02:06 PM

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PHAR 7633 Chapter 22

Bayesian Analysis of Clinical Data

Bayesian Analysis of Clinical Data

Monitoring drug disposition in patients can be challenging. Drug regimens may not be constant and only a small number of drug concentration sample may be available. Fortunately, the drug registration process requires extensive pharmacokinetic studies. Combining prior population pharmacokinetic data with a few data points from the patient of interest allows for a better understanding of the drug disposition in this patient. Bayesian pharmacokinetic analysis allows the integration of population information with patient data. The parameters of the pharmacokinetic model are adjusted to best-fit both the population and patient data. A different objective function is required to include both of these observations.

\[
\text{Objective Function} = \sum_{i=1}^{i=n} \frac{(Calc_i - Obs_i)^2}{\text{Variance}_i} + \sum_{j=1}^{j=m} \frac{(Calc_j - Pop_j)^2}{P\text{Variance}_j}
\]

Equation 22.4.1 Objective Function for Bayesian Optimization

Note the use of variance instead of weight in this objective function, Equation 22.4.1. Realistic values for the data variance (and thus weight) must be balanced with variance of each population parameter. The inclusion of patient data and population data provides the ability to estimate parameters in the patient for improved drug regimen recommendations.

In this section we will briefly describe how to set up one non-linear regression program, Boomer.

Program Set-up

As an example we can consider a patient given theophylline by IV infusion over 30 minutes. Population values for clearance, CL and V can be found in the text by Evans, Schentag and Jusko, 1992, chapter 13. Values of these parameters vary in patients with various disease states but for a 'normal' patients (70 Kg)) the values in Table 22.4.1 may be used as an example.
Table 22.4.1 Typical Parameter Values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean Value</th>
<th>Standard Deviation</th>
<th>Variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (L)</td>
<td>30.1</td>
<td>4.2</td>
<td>17.6</td>
</tr>
<tr>
<td>Clearance (L/hr)</td>
<td>3.61</td>
<td>1.47</td>
<td>2.16</td>
</tr>
</tbody>
</table>

Figure 22.4.1 Another Diagram Illustrating a One Compartment Model with an IV Infusion

After a dose of 1000 mg/hr for 30min (500 mg IV) samples were collected at 1 hr and 9hr after the start of the infusion. These samples were assayed and found to contain 15.6 and 5.8 mg/L, respectively. Assay standard deviations were estimated to be 5% of the value measured. These patient data and the population parameters from Table 22.4.1 were analyzed with Boomer using the Bayesian method. Figure 22.4.2 illustrates the resulting 'best-fit' to these two data points.

Figure 22.4.2 Linear Plot of Concentration versus Time
Analysis Type

The Bayesian method is specified early in the Boomer input stream.

METHOD OF ANALYSIS

0) Normal fitting
1) Bayesian
2) Simulation only
3) Iterative Reweighted Least Squares
4) Simulation with random error
5) Grid Search

-5) To perform Monte Carlo run (Only once at the start of BAT file)
-4) To perform multi-run (End of BAT file only)
-3) To run random number test subroutine
-2) To close (or open) .BAT file
-1) To finish

Enter choice (-3 to 5) 1

Figure 22.4.3 Specifying the Bayesian Analysis Method

Model Specification

Boomer doesn't include clearance as a parameter type so it must be entered as a type 19 (dummy) parameter. The elimination rate constant kel is specified as CL/V. Since volume (type 18) parameters cannot be specified before rate constants a dummy parameter Vd specified first. The model parameter V is simply set equal to Vd.

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Value</th>
<th>Type</th>
<th>From</th>
<th>To</th>
<th>Dep</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CL</td>
<td>= 3.613</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Vd</td>
<td>= 29.33</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>kel</td>
<td>= 0.1232</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>7001002</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>V</td>
<td>= 29.33</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>1002000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Duration</td>
<td>= 0.5000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>k0</td>
<td>= 1000.</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 22.4.4 Model Specification from the .OUT File

Data and Weight Specification

The two data points were entered from the keyboard with the weight specified by equation specifying a 5% standard deviation. A 5% standard deviation translates into a variance of 0.0025 x Observed Value. Thus the 'a' and 'b' values entered are 0.0025 and 2, respectively.
Weighting function entry for [Theophylline]

0) Equal weights
1) Weight by 1/Cp(i)
2) Weight by 1/Cp(i)^2
3) Weight by 1/a*Cp(i)^b
4) Weight by 1/(a + b*Cp(i)^c)
5) Weight by 1/((a+b*Cp(i)^c)*d^(tn-ti))

Data weight as a function of Cp(Obs)

Enter choice (0-5) 3
Enter a value 0.0025
Enter b value 2

Program Output

Figure 22.4.5 Specifying the Weight for the Data Points by Equation

Program Output

### Tabular and Statistical

** Tabular and Statistical **

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Value</th>
<th>S.D.</th>
<th>S.D. (Weight)</th>
<th>C.V. %</th>
<th>Weighted residual</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>CL</td>
<td>3.6134</td>
<td>0.904E-02</td>
<td>0.25</td>
<td>1.0</td>
<td>10.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.610</td>
<td>1.470</td>
<td>0.6803</td>
<td>0.2309E-02</td>
<td></td>
</tr>
<tr>
<td>2)</td>
<td>Vd</td>
<td>29.330</td>
<td>0.822E-01</td>
<td>0.28</td>
<td>1.0</td>
<td>0.10E+03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30.10</td>
<td>4.200</td>
<td>0.2381</td>
<td>-0.1833</td>
<td></td>
</tr>
</tbody>
</table>

Final WSS = 0.385777E-01 R^2 = 1.000 Corr. Coeff = 1.000
AIC = -2.51016 Log likelihood = 1.11 Schwartz Criteria = -5.12387
R and R^2 - jp1 1.00000 1.00000
R and R^2 - jp2 1.00000 1.00000
### (Section 4)

Data for [Theophylline] :-

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Value</th>
<th>Type</th>
<th>From</th>
<th>To</th>
<th>Dep</th>
<th>Start</th>
<th>Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CL</td>
<td>3.613</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Vd</td>
<td>29.33</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>kel</td>
<td>0.1232</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>7001002</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>V</td>
<td>29.33</td>
<td>18</td>
<td>1</td>
<td>1</td>
<td>1002000</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Duration</td>
<td>0.5000</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>k0</td>
<td>1000.</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Figure 22.4.6 Tabular and Statistical Output**

**Section 1** Preliminary Output describing the input/output details, the fitting (optimization) algorithm, integration method and weighting scheme.

**Section 2** Best-fit parameter values with statistical information are provided. The parameter CV values, the WSS, AIC and other values provide information about the model and how well the data have been fit to the model.

**Section 3** The model definition section provides the opportunity to confirm that the model has been described correctly.

**Section 4** The data are provided next as observed x and y values, calculated y values and weight and residual information. The observed data in this table should be checked against the correct values. Systematic differences between observed and calculated values may be detected in this section if the data analysis is incorrect.
Graphical

(Section 1)
Plots of observed (*) and calculated values (+) versus time for [Theophylline]. Superimposed points (X)

<table>
<thead>
<tr>
<th>16.53</th>
<th>Linear</th>
<th>16.53</th>
<th>Semi-log</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

0.000 <--- 12.  0.000 <--- 12.

(Section 2)
Plot of Std Wtd Residuals (X) versus time for [Theophylline] Plot of Std Wtd Residuals (X) versus log(calc Cp(i)) for [Theophylline]
Figure 22.3.8 Graphical Output provided by Boomer

(Section 1) A linear and semi-log printer-type plot of the observed and calculated y-values versus the x-values.

(Section 2) Standardized weighted residuals versus x-value or log(calculated y value) are very useful tools for detecting poor model or weighting scheme selection. Any obvious pattern in these plots should be explored as potential evidence of a poor fit to the data. Patterns are not as obvious with a typical Bayesian analysis since there are fewer observed data points.

The Boomer control file used in this analysis is provided here and the complete output file is provided here.

References


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PHAR 7633 Chapter 22

Non-Linear Regression Analysis of Population Data

Analysis using of Population Data using NONMEM

During the development of new drug entities (NDE) the manufacturer will study the disposition of the drug in numerous volunteers healthy and otherwise. The early, Phase I studies are typically conducted in healthy volunteers with the objective of determining the disposition characteristics of the NDE. These studies usually involve the collection of numerous blood and other samples from each subject. The data analysis techniques described earlier in this course may be quite useful for these studies. Later studies during Phase III involve the administration of the NDE to numerous patients who may be expected to have some therapeutic benefit from the NDE. These subjects may provide a wide range of covariates such as age, weight, sex, genetic characteristics, co-administration of other drugs and various clinical or pathological conditions. In these studies the protocol may provide for the collection of only one or two blood samples during various dosage regimens. It is difficult to analyse data separately to determine good estimate of the pharmacokinetic parameters. Fortunately there are data from a large number of subjects and there are a number of computer programs which are capable of analysing these data simultaneously.

One of these population pharmacokinetic (PopPK) computer programs is NONMEM. Other PopPK may be found here. NONMEM will allow the analyst to include data from many subjects in one analysis and provides estimates of the best-fit pharmacokinetic parameter values and estimates there variability (standard deviation or variance) between the subject as well as relationships with covariate values. The output from these analyses may be useful in the Bayesian estimate of clinical pharmacokinetic data as described earlier. The PopPK approach can also be used in cases of data rich sources, such as bioavailability studies, or sparse data information that might be available post-marketing during therapeutic drug monitoring.

Program Set-up

The use of NONMEM is aided by the use of NMTRAN, a pre-processing program. The user provides control and data files to NMTRAN which produces files required to compile, link and run NONMEM.

An example Control File

As an example we can consider some data simulated for ‘patients’ with varying renal functions. The subjects are given a drug by IV infusion and two blood samples were collected.

```
$PROBLEM Aminoglycoside example - Eta on Typical kel only
$INPUT ID AMT RATE TIME DV CRCL
$DATA TEST
$SUBROUTINES ADVANI
$PK

TA = THETA(1)
TB = THETA(2)
TK = TA*CRCL + TB
K = TK*(1 + ETA(1))
V = THETA(3)*(1 + ETA(2))
S1 = V

$ERROR

Y = F*(1 + ERR(1))
```

Figure 22.5.1 The Data and Model Specification for NONMEM

Here the data title and data format are specified on the first two lines. The data filename and the model subroutine are on the next two lines. The rest of this section describe model parameters K and S1 in terms of parameter (THETAs) and variability terms (ETAs). The data error or variance equation are defined as the parameter Y.
Parameter limits and initial values are specified in this section. Estimation limits, tabular and graphical output are specified later in this section.
### Data File Format

```
1 70 70 0.0 0.0 72.34
1 0.0 0.0 1.50 3.4272 72.34
1 0.0 0.0 8.00 0.4081 72.34
2 80 80 0.0 0.0 83.53
2 0.0 0.0 2.50 1.80792 83.53
2 0.0 0.0 9.60 0.05992 83.53
3 70 70 0.0 0.0 63.51
3 0.0 0.0 1.25 3.78868 63.51
3 0.0 0.0 9.60 0.22855 63.51
4 140 140 0.0 0.0 20.91
4 0.0 0.0 1.25 8.9859 20.91
```

**Figure 22.5.3 The Start of the Data File**

The data is input in tabular form as described above in Figure 22.5.1. The first column is the subject ID number. The next two columns provide the infusion amount and rate for the first of each three data lines. The fourth and fifth column input the time and value for each of the two samples and the final column specifies the creatinine clearance for this subject.

```
CUMULATIVE NO. OF FUNC. EVALS.: 179
PARAMETER: 0.98632E-01 0.1259E+00 0.9963E-01 -0.2210E-01 -0.9608E-02 -0.1539E-01
GRADIENT: -0.5364E+03 -0.3488E+02 0.2824E+03 0.6209E+01 0.2114E+03 0.1876E+03
ITERATION NO.: 25 OBJECTIVE VALUE: -0.1255E+04 NO. OF FUNC. EVALS.: 8

CUMULATIVE NO. OF FUNC. EVALS.: 219
PARAMETER: 0.98572E-01 0.1275E+00 0.9962E-01 -0.2210E-01 -0.9966E-02 -0.1528E-01
GRADIENT: -0.3265E+03 -0.1915E+02 0.9722E+02 -0.8242E+01 0.1142E+03 0.9623E+02
ITERATION NO.: 30 OBJECTIVE VALUE: -0.1255E+04 NO. OF FUNC. EVALS.: 0

CUMULATIVE NO. OF FUNC. EVALS.: 278
PARAMETER: 0.9887E-01 0.1216E+00 0.9986E-01 -0.2214E-01 -0.1024E-01 -0.1517E-01
GRADIENT: 0.1829E+02 0.3513E+00 -0.5171E+02 -0.1679E+02 -0.7762E+00 -0.1330E+00

MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED: 278
NO. OF SIG. DIGITS IN FINAL EST.: 3.4
```

**Figure 22.5.4 Progress during and toward the End of the Iterative Process**
Tabular Output

MINIMUM VALUE OF OBJECTIVE FUNCTION  -1255.007

FINAL PARAMETER ESTIMATE

THETA - VECTOR OF FIXED EFFECTS

<table>
<thead>
<tr>
<th>TH</th>
<th>TH 2</th>
<th>TH 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.89E-03</td>
<td>1.40E-02</td>
<td>1.50E+01</td>
</tr>
</tbody>
</table>

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS

<table>
<thead>
<tr>
<th>ETA1</th>
<th>ETA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.31E-03</td>
<td>&lt;- 9.9 %</td>
</tr>
<tr>
<td>0.00E+00</td>
<td>2.10E-03</td>
</tr>
</tbody>
</table>

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS

<table>
<thead>
<tr>
<th>EPS1</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.60E-03</td>
</tr>
</tbody>
</table>

Figure 22.5.5 Final Parameter Values

The TH values refer to the THETA parameters described in Figure 22.5.1 for slope (TA) and intercept (TB) of the kel (K) equation and volume, V. Two ETA values and one EPS1 value are also output in this section. These values provide an estimate of the uncertainty in the parameters and the data values. Other tabular output would include time, observed and calculated data (not shown).
Graphical Output

A variety of graphical output is also possible including observed versus calculated data, Figure 22.5.6 and weighted residual versus the observed value, Figure 22.5.7.

Figure 22.5.6 Observed Data versus Calculated Data
Figure 22.5.7 Weighted Residual versus Concentration

Notice the scatter of points above and below the horizontal zero line.