NONMEM Users Guide -- Part I

Users Basic Guide

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Preface to 3rd Edition

The appearance of this 3rd edition of the Users Basic Guide coincides with the appearance of NONMEM 77 Version III Level 1. The 2nd edition was written before NONMEM 77 was developed, and its appearance coincided with that of Version II of the earlier IBM-specific NONMEM. Therefore, much has happened to the NONMEM program since the 2nd edition which should be documented in the Users Basic Guide, and this 3rd edition achieves this goal. In addition, with this edition there are many changes to the document which substantially improve its readability and clarity. However, the organization and examples used in the 3rd edition are little changed from those used in the 2nd edition.

The IBM-specific NONMEM has not been distributed since it was superceded in 1984 by NONMEM 77, a program that can be used with any machine with an ANSI FORTRAN 77 compiler. There is not as much opportunity today as there was earlier to confuse these two programs, and so there is not as much necessity when referring to the current program to follow the name 'NONMEM' with the term '77'. Consequently, with the appearance of Version III of NONMEM 77 it will henceforth be called simply NONMEM, and this practice is reflected in this 3rd edition of the Users Basic Guide.

The new features in Version III are:

1. The problem summary has been streamlined.
2. NONMEM can provide some help in obtaining initial estimates for θ, Ω and Σ.
3. The appearance of any given task specification record is optional.
4. Tables can be either printed or stored in (machine-readable) files.
5. A new task can be performed which simulates data according to the user-specified model. This data can be analyzed by performing the estimation, covariance, tables and scatterplot tasks.
6. The objective function can be partly defined by user-code.

Features 1-4 are described in this Guide. Features 5-6 are described in the 2nd edition of NONMEM Users Guide, Part II, whose appearance also coincides with the appearance of Version III.

It is advisable that a new NONMEM user read this Guide and try running and understanding some or all of the examples found herein. The user can check that he has correctly installed the program by comparing the output he obtains with the output displayed in this document. There might be some rather small discrepancies in so far as the computations are somewhat machine dependent. All the output in this Guide is obtained using a SUN model 2, equipped with a SKY floating-point coprocessor and running SUN UNIX 4.2 Release 3.4. All the output is obtained using Double Precision NONMEM; see section A.1.

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A. Introduction and General Background

A.1. The NONMEM Program

The NONMEM Project is an undertaking by researchers in the Schools of Medicine and Pharmacy of the University of California, San Francisco. The project is a continually evolving one, aimed at providing methodological results and computer tools for the analysis of data that may be described by regression type models with mixed effects, i.e. both fixed *and* random effects, any of which may enter the model nonlinearly. Data of this sort arise frequently in clinical pharmacological projects, and to various degrees in other scientific fields. They arise when there are multiple (or repeated) measurements taken on a number of experimental units.

Version III Level 1 of NONMEM, a computer program to analyze data using a **n**onlinear **m**ixed **e**ffects **m**odel, is now being distributed. It is written in ANSI FORTRAN 77. It is reliable, and attention has been paid to the input of control information, to the output of results, and to program diagnostics. The inputs to the program consist of data files, control information, and user-coded subroutines. The required formats for these inputs are not, however, user-friendly. The NONMEM Project has paid more attention to the development of more important aspects of the program - that is until recently. At the same time as Version III is being distributed the NONMEM Project is also distributing for the first time another program, NM-TRAN, a preprocessor to NONMEM that translates inputs specified in a more user-friendly way to the formats required by NONMEM. This translator is documented in NONMEM Users Guide IV, NM-TRAN Guide. Also, much effort has been made to make NONMEM efficient. However, this efficiency is measured with respect to the types of computationally intensive tasks the program performs, tasks that sometimes call for using a large-scale computer, or a smaller dedicated machine.

Versions I-III incorporate an important methodological restriction. Although fixed effects may enter the model nonlinearly, random effects must enter the model linearly. Therefore, the goal described at the beginning of this section is not fully met. However, if a model is contemplated in which some random effects enter nonlinearly, it may often be approximated well-enough by a model in which all random effects enter linearly. This approximation is described in a number of references (Sheiner et al 1977, Beal, 1984a), as well as being illustrated in chapter F of this document. Research is in progress within the NONMEM Project that could lead to a future version of NONMEM in which this restriction is relaxed. Except for the example discussed in chapter F, all the examples in this document involve linearly occuring random effects.

Another program restriction concerns the number of possible levels of nesting of the random effects. NONMEM provides only one level of nesting. With one level of nesting there is one group of random effects and another group nested within the first group. This is usually adequate for pharmacokinetic and pharmacodynamic applications. One advantage of NONMEM over other programs for mixed effects models is that the random effects in the first group can be multivariate, and the random effects in the second group can be multivariate.

There really are two NONMEM programs, single- and double-precision versions. The user can choose to use either. Many problems with few parameters to be estimated can be run successfully with the single-precision version. Problems with many parameters usually need double-precision arithmetic. If the computational time requirement does not pose a particularly difficult problem, the user should simply use the double-precision version. This version is not simply the single-precision version with all floating-point variables and arrays declared double precision. Rather, care has been taken to use double-precision only where it is necessary. When the computational time requirement does pose a problem, the user might first try using single-precision. If a problem develops (see section C.3.5.1), then the user might try using double-precision.

A.2. Purpose and Organization of the Document

This document, the Users Basic Guide, is first of a six part series of user documentation for the NONMEM system. The other five parts are:

Part II - Users Supplemental Guide
Part III - NONMEM Installation Guide
Part IV - NM-TRAN Guide
Part V - NONMEM-PREDPP Introductory Guide
Part VI - PREDPP Guide

This first part contains the essential information about how to use NONMEM. It is presumed that the reader has had some previous experience with using a nonlinear regresssion type program and that he knows how to interpret the output from that program.

Part II contains supplemental information about using NONMEM, and Part III contains program installation information and describes the program file structure. Part IV is a reference guide for NM-TRAN (see section A.1). Part V is a primer designed for beginning users who wish to use NONMEM for analyzing pharmacokinetic data. For such users it might be helpful to begin by reading Part V, rather than this document. Part VI contains detailed user-information about PREDPP, a useful software package to be used with NONMEM by those analyzing pharmacokinetic data.

The Users Basic Guide is organized around realistic examples, progressing from a simple nonlinear regression example to an example of a nonlinear model with several one-level nested random effects. These examples are taken from the field of Clinical Pharmacology. Thus those persons who are not very familiar with nonlinear mixed effects models may, by carefully following this progression of ideas, become more familiar with the concepts. Presumably though, a NONMEM user is familiar with simple nonlinear regression and has some familiarity with mixed effects models; he understands that he is faced with data manifesting several variance components, and he knows how to begin to model his data in terms of these components. As stated above, for the beginner with pharmcokinetic data it might be helpful to first study NONMEM Users Guide, Part V. With each example the inputs and outputs of the program that pertain to that example and that are not clear from the previous examples, are explained. The experienced NONMEM user should be helped by the Appendix which summarizes the program's control records.

A.3. NONMEM Features

The important ability of NONMEM to help analyze complicated statistical regression type models has already been noted in section A.1. Other features of the program are briefly listed here.

i Derivatives of the regression function and certain weighting functions with respect to model parameters need not be supplied.

ii The estimates of fixed effect parameters may be constrained.

iii Initial estimates of the parameters to be estimated need not be given.

iv The iterative search involved in obtaining the final parameter estimates has good convergence behaviour even when parameter estimates are constrained under a null hypothesis.

v A file may be output at the end of the search that allows the search to be conveniently and smoothly continued (or computations depending on the results of this search to be performed) in a subsequent run, without once again starting the search from the beginning.

vi An estimate of the covariance matrix of the (parameter) estimate is carefully computed.

vii Tables and scatterplots of data items, and also of predictions, residuals, and weighted residuals, may be output.

viii The amount of data that may be input is not limited.

ix Multiple problems may be implemented during a single NONMEM run.

Elaboration of some of these features occurs in section A.4 below; all are treated in detail in chapters C-F. Other less frequently used features that are described in NONMEM Users Guide Part II are:

x Variance-covariance components may also be constrained in certain ways.

xi There is considerable flexibility in defining the objective function.

xii Transgeneration of the data may occur before and after parameter estimates are obtained.

xiii Data may be simulated (as well as subsequently analyzed) under the specified model.

xiv Eigenvalues of the estimated correlation matrix of the (parameter) estimate may be computed.

One simple constraint on covariance components, i.e. constraining all of these to be zero, is described in Part I.

A.4. Major NONMEM Tasks

There are six major NONMEM tasks that may be undertaken in any given NONMEM problem. These six tasks are performed in what are called the six program steps. Each of these steps are optional, though some step depend on the results of previous steps.

In the first step, the Simulation Step, data are simulated under the user-specified model. The particulars of this step are discussed in NONMEM Users Guide, Part II.

In the second step, the Initial Estimation Step, initial estimates of model parameters are computed. Initial estimates may be specified by the user, and often this is not difficult. But on occasion some help is needed, and the user may leave any particular initial estimate blank, in which case the Initial Estimation Step is executed.

In the third step, the Estimation Step, final estimates of the model parameters - fixed effect parameters and variance-covariance components - are obtained. For this purpose an objective function (e.g. a least squares objective function) in the model parameters is minimized, and the final estimate (as a vector) is taken to be the minimum point. The minimization is carried out by implementing a numerical search in parameter space for the minimum point. Actually, NONMEM reparametrizes the model, the objective function is expressed internally in terms of the new parameters, and the search is implemented in the transformed parameter space. The default objective function is the extended least squares objective function (Beal, 1984a,b) which is often appropriate with continuous-valued type observations modeled in terms of a regression function whose values predict these observations. There can be other types of observations, e.g. dichotomous observations or failure-time observations, where another objective function would be more appropriate. NONMEM allows the user to define many other types of objective functions.

The numerical search is implemented according to an algorithm by R.A. Fletcher, 1972, modified by IMSL (whose code forms the basis for the NONMEM code), and further modified by the NONMEM Project. This algorithm is a derivative-free quasi-Newton type minimzation algorithm for an arbitrary objective function. It is presumed that the user has some familiarity with the types of numerical problems that can be encountered with minimization algorithms.

In the fourth step, the Covariance Step, an estimate for the covariance matrix of the estimate obtained in the Estimation Step is computed. The accuracy of this covariance estimate increases as the number of (statistically independent) observations increases. It is not a simple matter to know how reliable the covariance estimate is for any given problem. This difficulty is encountered with any nonlinear regression program. The examples used in this document involve only moderate amounts of data, but in this respect they are similar to many problems run over the years by NONMEM users. On the other hand, the original impetus for the NONMEM Project was to develop an ability to analyze large quantities

of pharmacokinetic data arising during routine patient care, and the large data requirement underlying the covariance estimate would not be a particular problem in this context. In any case, some elements of the covariance estimate may be better estimated than others. This goes along with the fact that some model parameters may be better estimated than others. For example, parameters in the regression function are usually estimated better than variance components, and variance components are usually estimated better than covariance components. The covariance estimate at least provides certain important qualitative information. In this document it is called the covariance matrix, for short, and the square roots of its diagonal elements are the estimates of the standard errors of the parameter estimates.

The covariance matrix involves derivatives of the objective function with respect to model parameters. These derivatives are computed numerically, using a complex algorithm based in part on the method described by Nelder and Mead (1964). In addition to computations of the covariance matrix, computations of the inverse covariance matrix, the standard error estimates, the correlation matrix (derived from the covariance matrix), and the eigenvalues of the correlation matrix are all performed in the Covariance Step.

In the fifth step, the Tables Step, all data items of selected types may be tabulated. There can be several tables, and each table can be printed or stored in a file. Each row of a table corresponds to a different data record, and each column corresponds to a different type of data item. With each data record there are three additional types of data items, called the NONMEM generated data items, which do not occur in the data set itself, but they are included in all tables. As do the other data items in the data record, these three data items relate to the observation in the data record. With the default objective function (i.e. the extended least squares objective function) these three data items are: the prediction of the observation, the residual difference between observation and prediction, and the weighted residual difference. With other user-defined objective functions, other NONMEM generated data items can be defined. Also, the rows of a table may be sorted on the data items of one type, and then sorted within that sorting on the data items of another type, etc.

In the sixth step, the Scatterplot Step, data items of one type can be scatterplotted against the data items of another type. A scatterplot can be used to plot functions as well as relationships that show "scatter". A scatterplot of y vs x may also include the line y=x (useful when prediction is scatterplotted against observation), and a scatterplot of residual or weighted residual data items always includes the "zero line". Moreover, families of scatterplots of y vs x may be generated. Each member of a family is obtained using only the data records with the same value of some third data item type, u. A family member exists for each different value of u occuring in the data set. In addition, families, each of whose members is obtained using only the data records with the same values of some third and fourth data item types, u and v, may also be generated. Using the transgeneration feature (see NONMEM Users Guide, Part II), data items to be tabled or scatterplotted may be defined in terms of the final parameter estimate.

A.5. Random Interindividual Effects

Typically with population type pharmacokinetic data, there are repeated observations, i.e. measured responses, on each of a number of experimental units. The experimental units are animal or human subjects, and presumably, they are chosen randomly from the population of interest. If there were no measurement error in the responses, and if for fixed values for a set of measurable independent variables, a subject always had the same response, then usually, one would still not be able to predict this response with full certainty. This is because there are usually intersubject, or what we call interindividual, differences in response which cannot be explained solely in terms of the measureable independent variables. Rather, they are attributable to effects whose values are unknown and which we treat as random, and we call these effects random interindividual effects. The rationale for treating these effects as random is that as individuals are randomly chosen, so are the interindividual values associated with the effects in question. The values of a random interindividual effect are constant for all observations from a given individual. In the context of NONMEM the values of a random interindividual effect, as they vary from individ-

ual to individual, are to be regarded as being statistically independent. The rationale for this is that individuals are assumed to be chosen not only randomly but also *independently* one from the other. The values of random interindividual effects are unknown. Fixed interindividual effects are the effects whose values can be measured. (These need not be treated as random, and so they are regarded as *fixed.)* The concept of random interindividual effects is central to NONMEM. This concept sets the program apart from other nonlinear regression programs but makes it similar to other repeated measures type programs.

With models where no random effect is nested within another random effect, NONMEM treats all random effects as random interindividual effects. In other words, the values of all random effects vary only from individual to individual. Consider, for example, any simple nonlinear regression model. There is no nesting of random effects since the model has only one random effect (statistical residual effect). The value of this effect varies from observation to observation, but each observation can be identified with a different individual. Either each observation indeed comes from a different individual, or when the observations do not come from different individuals, because these observations are regarded as being statistically independent, then for the purposes of modeling, they can be regarded as coming from different individuals. (In the latter case, and when all observations indeed come from a single individual, the population about which inference is made is, of course, this individual.) Therefore, the random effect can be (and with NONMEM it is) treated as a random interindividual effect.

With models where there is a one-level nesting of random effects NONMEM treats the random effects in the group at the outside of the nest as random interindividual effects. NONMEM treats the random effects in the nested group as random intraindividual effects. Their values vary from observation to observation within an individual. In this context by an observation we mean either a univariate observation, or, when appropriate, a multivariate observation.

The random interindividual effects are denoted by η_1, η_2, etc. Their variance-covariance matrix is denoted by Ω and is called OMEGA in the NONMEM printout. The random intraindividual effects are denoted by ε_1, ε_2, etc. Their variance-covariance matrix is denoted by Σ and is called SIGMA in the NONMEM printout.

A.6. Acknowledgements

Many scientists have worked closely with the NONMEM Project Group, and by using NONMEM and providing helpful feedback, have greatly contributed to its development. Many NONMEM users have on occasion also shared their experience. We hope that the user-community will continue to feel free to report successes and failures so that the program can be further evaluated and modified in ways from which everyone can benefit.

IMSL has also greatly contributed to NONMEM development by entering into an agreement with the NONMEM Project wherein some IMSL proprietary software can be incorporated into the NONMEM system.

The examples used in this document involve theophylline data that was kindly contributed for this purpose by Drs. Sidney Riegelman and Robert Upton.

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B. Data, Control, and File Records

B.1. Data Records

The data set consists of a sequence of data records, essentially one for each different observation (although see the discussion below about data records with missing dependent variable data items). A data record, in turn, is a sequence of data items (the same number of data items in each data record). One of these data items is the associated observation, also called the dependent variable (DV) data item. The other data items in the data record may be loosely regarded as specific items needed to predict the DV data item under the user-specified statistical model. The data items of each data record are placed on a number of contiguous FORTAN records, and this set of FORTRAN records is read by NONMEM as a unit, i.e. with a single I/O list, under a user-supplied FORTRAN format specification. The format specification may consist of E, F, and X format codes. An I code is not allowed. For example there may be nine data items per data record, and these may be distributed over two FORTRAN records.

Example B.1.i:

```
1.2   3.6   4.7   .27E01          Record 1

0.5   9.8   6.5   .12E00   3      Record 2
```

and read with the format specification (3(F3.1,2X),E6.2/3(F3.1,2X),E6.2,2X,F1.0).

In NONMEM the data records with DV data items associated with a given individual are grouped together. This is accomplished in part by including in each data record a data item identifying the individual with which the DV data item in the record is associated. This data item is called the identification (ID) data item. An ID data must always appear in the data record, except when every data record would ordinarily have a *different* ID data item, in which case the ID data items are not necessary. In the above example the ninth data item might be the ID data item, although there is no requirement that the ID data item be integer-valued. The grouping of the data records is acomplished by including ID data items in the data records *and* by arranging that all data records with the same ID data item be contiguous in the data set. Two or more data records are understood to be contiguous if the sets of FORTRAN records on which the data items of these data records are placed (one set of FORTAN records per data record) occur contiguously in the data file. The data records with the same ID data item are collectively called an individual record. This ID data item is also called the ID data item of the individual record.

ID data items can be constructed with a little more flexibility than indicated above. The ID data item of an individual record A must differ from that of the following individual record B. However, it can be the same as the ID data item of the individual record following B. The rule is that only the two ID data items of two contiguous individual records must differ.

As mentioned in section A.5, when the statistical model has non-nested random effects, the observations are regarded as arising from different individuals, even if, indeed, they do not. The observations in simple nonlinear regression models, for example, are so regarded. In this situation each data record containing an observation should be contained in a different individual record.

Data records may be designated as missing DV data items. Such records are useful for a variety of reasons. For example, suppose that the prediction of the DV data item depends on the value of time, another data item in the data record. Suppose also that one wants to plot predictions vs time, and for this purpose, one wants to develop predictions at time points other than those for which there correspond DV data items in the data set. One can construct additional data records with these time points and designate them as missing DV data items. Predictions will be generated for these data records, and these predictions can appear in tables and be used in scatterplots. There will be DV data items on these records, but they will be "dummy" items. The user can let them be zero or any other value(s). NONMEM will not

use the DV data items on these records - not for the purpose of estimation. However, all data items on all records will be used for the purpose of constructing tables. For the purpose of constructing a scatterplot where one of the axes of the plot corresponds to the DV data item, or the residual data item, or the weighted residual data item, data records designated as missing the DV data item are not used.

If there are to be data records designated as missing DV data items, then all data records must have a missing DV (MDV) data item. A MDV data item must be either zero or one. A zero MDV data item means that the DV data item in the record is not missing; a one means that it is missing. If there are MDV data items, there must also be ID data items (even if there is but one data record in each individual record). A data record with MDV data item equal to zero is called an observation record. When there are no MDV data items in the data set, all data records are observation records. An individual record need not have any observation records; that is, it may be comprised only of data records designated as missing DV data items.

In a model with one-level nested random effects there are random interindividual effects, and nested within them, there are random intraindividual effects. The random interindividual effects may be called random level-one effects, and the random intraindividual effects may be called random level-two effects. (There are two levels of random effects, *but* there is only one level of nesting.) In a statistical model for the DV data items, the values of random level-one effects are different only for DV data items in different individual records. The ID data items are used to group data records into individual records. The ID data item is also called the level-one (L1) data item, and an individual record is also called a level-one record. Now suppose that multivariate observations are obtained from each of a number of individuals. In the statistical model the values of random level-two effects are different only for DV data items that are elements of different observations. (If all observations are univariate, the values of random level-two effects are different for all DV data items.) Therefore, when there are multivariate observations modeled with one-level nested random effects, another type of data item must be used to group data records according to the observations with which their DV data items are associated. This data item is called the level-two (L2) data item. The grouping of the data records by observation is accomplished by including L2 data items in the data records *and* by arranging that all data records related by the same L2 data item be contiguous in the data set. The data records related by the same L2 data item are collectively called a level-two record. This L2 data item is also called the L2 data item of the level-two record. Obviously, a level-two record should be totally contained within a level-one record.

L2 data items can be constructed with a little more flexibility than indicated above. The L2 data item of a level-two record A must differ from that of the following level-two record B. However, it can be the same as the L2 data item of the level-two record following B. The rule is that only the two L2 data items of two contiguous level-two records must differ.

The DV, ID, MDV, and L2 data items are the data items in the data set that are of particular concern to NONMEM, and they are called the NONMEM data items. Other data items in the data set are of concern only to user-supplied subprograms.

B.2. Control Records

The control records contain the instructions to NONMEM. The sequence of control records is called the control stream. Each control record is comprised of one or more FORTRAN 80 character records. All control records begin with a 4 character preface such as ESTM, SCAT, and THTA (abbreviating ESTIMATION, SCATTERPLOT, and THETA, respectively). The fields on a control record begin in position 9, except where noted otherwise. If a control record needs to be continued on more than one FORTRAN record, the fields on each of the continuation records begin in position 9 also, and the first 8 positions are left blank.

Example B.2.i:

```
        THTA    1.1     2.2     3.3  ...  9.9

                10.10   11.11   (continuation record)
column no.:     9       1       2       7
                        7       5       2
```

Some control records have only one field, 72 characters long, in which a character string is placed. Such records are said to have character format. They cannot be continued.

Example B.2.ii

```
        PROB    THE THEOPHYLLINE DATA
column no.:     9
```

Most control records have one or more 4 character fields in which integers are placed. These integers are to be right-adjusted in the fields. This type of control record has at most 18 fields per FORTRAN record. Such records are said to have integer format.

Example B.2.iii:

```
        SCAT    0   2
column no:      1   1
                2   6
```

Some control records, like that in Example B.2.i above, have one or more 8 character fields in which FORTRAN fixed point numbers are placed. This type of control record has at most 9 fields per FORTRAN record. Such records are said to have fixed point format.

There are 21 functional types of control records, as listed in Table B.2.i. However, many of these are optional.

Table B.2.i
Control Record Types

Record type	Preface
FILE record	FILE
PROBLEM record	PROB
DATA record	DATA
ITEM record	ITEM
INDEX record	INDX
LABEL record	LABL
FORMAT record	FORM
FIND record	FIND
STRUCTURE record(s)	STRC
THETA CONSTRAINT record	THCN
THETA record	THTA
LOWER BOUND record	LOWR
UPPER BOUND record	UPPR
DIAGONAL record(s)	DIAG
BLOCK SET record(s)	BLST
SIMULATION record	SIML
SOURCE record(s)	SORC
ESTIMATION record	ESTM
COVARIANCE record	COVR
TABLE record(s)	TABL
SCATTERPLOT record(s)	SCAT

The record types are divided into five major groups. The first group is comprised of the FILE and PROBLEM records. The second group is comprised of the data set specification records; these records define the characteristics of the data set. The third group is comprised of the model specification records; these records, along with the user-supplied subroutine PRED, define the simulation/data-analytic model. The fourth group is comprised of the initial estimate records; these records give the initial parameter estimates, or information that can be used to obtain these estimates. They also may contain information that can be used to obtain final parameter estimates. The fifth group is comprised of the task specification records; these records define the tasks that are to be implemented in order to simulate/analyze the data.

B.3. File Records

The control stream is stored in a file. There are other files used by NONMEM (for a complete listing of these see NONMEM Users Guide III). For example, the data set can be stored in a separate file. (The data set can also be "embedded in the control stream", in which case it is effectively stored in the file containing the control stream.) The file mentioned in point v of section A.3 is another example. It is called a Model Specification File. Each of these two examples is an example of a file that exists at the user's option (unlike the file containing the control stream) and that must be opened by NONMEM itself, i.e. instructions to open the file must be given to NONMEM. This type of a file is called an optional NONMEM file. (There may be files that are opened by user-supplied subroutines. These are regarded differently. For discussion of these see NONMEM Users Guide, Part II.)

The file records contain the instructions to open the optional NONMEM files. The sequence of file records is called the file stream. Each file record is formatted exactly like a character-formatted control record (see above), with the exception of the problem delimiter record. The name of a file is placed in the character field (left adjusted). There are 4 functional types of file records, as listed in Table B.3.i.

Table B.3.i
File Record Types

Record type	Preface
DATA record	DATA
MODEL SPECIFICATION FILE INPUT record	MSFI
MODEL SPECIFICATION FILE OUTPUT record	MSFO
TABLE record	TABL

All these records are optional. They may occur in any order, with the one exception that when a MODEL SPECIFICATION FILE INPUT record and MODEL SPECIFICATION FILE OUTPUT record both occur for the same problem, the latter must preceed the former. There can be only one file record of each type per problem. The file records for any one problem must be followed by a problem delimiter record, i.e. a record consisting of asterisks in positions 1-4. If there are no file records with a problem, only the problem delimiter record should appear.

When the data set is contained in a separate file, the name of this file is placed in the field of the DATA record. A Model Specification File occurs in two ways, as a file to be input when continuing a search, and as a file to be output to allow a search to be continued later. The MODEL SPECIFICATION FILE INPUT record and the MODEL SPECIFICATION FILE OUTPUT record correspond to these two files; the name of the file is placed in the field of the corresponding record. Each table generated in a given problem may be stored in a common file called a Table File The name of the Table File is placed in the field of the TABLE record.

C. Simple Nonlinear Regression

C.1. An Example

Although the main purpose of NONMEM is to handle more complicated statistical models than the simple nonlinear statistical regression model, the example discussed in this chapter will help illustrate and explain many aspects of NONMEM. Also, since some of the features illustrated in this chapter are not part of every nonlinear regression program, the user may be interested in using NONMEM with simple nonlinear regression models. These features include the ones listed as i-ix in section A.3. The features listed as x-xiv (not illustrated in this chapter) could also apply to simple nonlinear regression.

Typical of a simple nonlinear regression situation is the one discussed here where the plasma concentation of the drug theophylline has been observed at various times after an oral dose has been administered to a subject. The regression function is taken to be the "one-compartment model with first-order absorption" (Gibaldi and Perrier, 1982):

$$f(\theta_1, \theta_2, \theta_3, x_1, x_2) = \frac{\theta_1 x_1}{\theta_3(\theta_1 - \theta_2)} (\exp(-\theta_2 x_2) - (\exp(-\theta_1 x_2))$$

where there are three regression parameters, θ_1, θ_2, and θ_3, and two independent variables: x_1, which denotes the amount of the dose, and x_2, which denotes time. The simple nature of the situation refers to the statistical model which is defined by

$$y_i = f(\theta_1, \theta_2, \theta_3, x_{1i}, x_{2i}) + \eta_i$$

where y_i is the ith value of the dependent variable, x_{1i} and x_{2i} are the associated values of the independent variables (x_1 is subscripted here, although its value remains constant), and the η_i are statistically independent random errors with means 0 and common variance σ^2. This variance is another model parameter which is to be estimated. Note that the variance of y_i is also the constant σ^2.

To proceed with the data analysis one needs to inform NONMEM about

i the organization of the data set

ii some underlying model structure: in this case the number of regression parameters and the fact that there is only one random effect

iii the way to compute values of the regression function

iv initial estimates of the model parameters

v the tasks to be performed

The data set specification records take care of i, the model specfication records take care of ii, the initial estimate records take care of iv, and the task specification records take care of v. A user-supplied FORTRAN subprogram, PRED, takes care of iii. These four sources of input will be discussed in the remaining sections of this chapter. Before turning to this discussion, some remarks about estimation with simple nonlinear regression are in order.

Traditionally, estimates of the regression parameters are obtained by searching for those values $\hat{\theta}_1$, $\hat{\theta}_2$, $\hat{\theta}_3$, of the parameters that minimize the function

$$O(\theta_1, \theta_2, \theta_3) = \sum_{i=1}^{I} (y_i - f(\theta_1, \theta_2, \theta_3, x_{1i}, x_{2i}))^2$$

where I is the number of observations. Such a function is called an objective function. This particular function is called the least squares (LS) objective function. The estimate $\hat{\sigma}^2$ of σ^2 is obtained by dividing the minimum value of the objective function by I (or sometimes by I minus the number of regression parameters, i.e. I-3 in this case). For simple nonlinear regression, NONMEM uses a slightly different ob-

jective function:

$$O(\theta_1, \theta_2, \theta_3, \sigma^2) = I \log \sigma^2 + \sum_{i=1}^{I} (y_i - f(\theta_1, \theta_2, \theta_3, x_{1i}, x_{2i}))^2/\sigma^2$$

and takes the values $\bar{\theta}_1$, $\bar{\theta}_2$, $\bar{\theta}_3$, $\bar{\sigma}^2$ of the four model parameters minimizing this function to be the parameter estimates. However, it may be easily verified that

$$\bar{\theta}_1 = \hat{\theta}_1, \quad \bar{\theta}_2 = \hat{\theta}_2, \quad \bar{\theta}_3 = \hat{\theta}_3, \quad \bar{\sigma}^2 = \hat{\sigma}^2.$$

This objective function is called the extended least squares (ELS) objective function. It is a special case of a more general ELS objective function described in later chapters. This general objective function is used by default with NONMEM because it can be used with statistical models that are more complicated than a simple nonlinear regression model, while, as just noted, a special case of it can also be used to obtain simple least squares estimates. In its general form use of the ELS objective function provides statistically consistent estimates under the assumption that the data arise from the data analytic model (Beal, 1984b). With simple nonlinear regression models, or with different models, different objective functions from this default function may be used to obtain parameter estimates (see NONMEM Users Guide, Part II).

C.2. PRED

The regression function f is computed for various values of the regression parameters and independent variables. The user-supplied subroutine PRED is expected to return the appropriate value of f for any such set of values. The argument list for PRED is

ICALL, NEWIND, THETA, DATREC, INDXS, F, G, H.

The arguments ICALL and INDXS are discussed in sections C.4.2 and C.4.1, respectively. The argument NEWIND is discussed in section C.3.5.2. The argument H is discussed in chapters E and F. THETA is a one-dimensional array in which the values of the θ's are passed. DATREC is another one-dimensional array in which a data record is passed, including, in our example, the data items corresponding to the values x_{1i} and x_{2i}, for some i, of the independent variables. PRED is called many times, and when it is called, it is called in bursts. During a burst of calls, the values in THETA are held fixed, and the data records from an individual record are passed one after the other in the order in which they appear in the individual record. This is called a burst of the individual record. In the example ID data items are not used, and so every data record is an individual record. In this case every burst of an individual record will consist of a single call.

Using the values in THETA and DATREC, PRED must compute the value of f and return it in the argument F. This is illustrated in Fig. 1, where one possible code for a PRED which implements the example is given. With simple nonlinear regression the value 1.0 must be returned in the first entry of the one-dimensional array G. The reason for this is made clearer in chapter D.

The PRED subroutine may be as complicated as is needed. In particular, it may call other user-supplied subroutines to accomplish various tasks. The following dimension statement should always be included:

```
DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
```

as well as the statement:

```
DOUBLE PRECISION THETA,F,G,H
```

when Double Precision NONMEM is being used. When double precision is used, the floating-point computations in PRED based on the values in THETA should be done in double precision. Failure to do so can result in failure to estimate the parameters altogether.

C.3. Control Records

C.3.1. Introduction

The first control record in the control stream must be the FILE record, a record that applies to all the problems occuring in the NONMEM run. This record is not to be confused with a file record appearing in the file stream. However, this record is very much concerned with file records. Character format is used. The character field contains the name (left-adjusted) of a file containing the file stream. If no file records are to be used (meaning that no optional NONMEM files are to be used), then the word NULL can be placed in the field, and it is then understood that there is no file stream. See, for example, the control stream shown in Fig. 2.

A problem specification is a sequence of control records providing the control information for a given problem. The control records are chosen from the list given in Table B.2.i (but cannot include the FILE record), and the order in which they appear in the problem specification must follow the order in which they appear in the table. A NONMEM run can consist of a single problem. A control stream is constructed which consists of the FILE record followed by a problem specification. This is illustrated by the control stream in Fig. 2. Multiple problems can occur in a single NONMEM run simply by constructing a control stream consisting of the FILE record followed by the concatenation of a number of problem specifications.

The first control record of a problem specification must always be the PROBLEM record. Character format is used. A heading for the computer printout is placed in the field. See Fig. 2. The next four control records of the problem specification in that figure are data set specification records, the DATA, ITEM, LABEL, and FORMAT records. These are discussed in section C.3.2. The next record is a model specification record, the initial STRUCTURE record. This is discussed in section C.3.3. The next five records are initial estimate records, the THETA CONSTRAINT, THETA, LOWER, UPPER, and DIAGONAL records. These are discussed in section C.3.4. The last five records are task specification records, the ESTIMATION, COVARIANCE, TABLE, and SCATTERPLOT records. These are discussed in section C.3.5. This entire discussion is summarized in the Appendix.

The entire computer printout which results from using the PRED routine and control stream given in Figs. 1 and 2, respectively, is given in Figs. 3-18. Explanation about this printout is given below along with detailed explanation about the control records. The first page of printout is a rather self-explanatory page summarizing the information given in the problem specification. It is called the problem summary.

C.3.2. Data Set Specification Records

C.3.2.1. DATA Record

Control parameters giving a global characterization of the data set are given in the DATA record. This record must appear in a problem specification. Integer format is used.

The data set may be embedded in the control stream as in Fig. 2. If the number of data records is small, this is often the most convenient procedure. Then a blank or 0 is placed in field 1, and a blank or 0 is placed in field 2.

Alternatively, the data set may be contained in a separate (sequential) file, in which case a 1 is placed in field 1. With the first problem the file is read once only, until all data records in the data set are read. NONMEM knows when to stop reading data records because the number of data records is placed in field 3. If there is a subsequent problem which uses the same data set, the file will need to be rewound

before it can be read again. This is accomplished by placing a 1 in field 2. If a subsequent problem in the same run uses a second data set, one contained in the same file as is the first data set and placed immediately after it, then with this subsequent problem the file should not be rewound. The reading of the file must continue from where it ended with the first problem. This is accomplished by placing a 0 or blank in field 2.

As stated above, the number of data records in the data set is placed in field 3. With large data sets, it may not be convenient to have to know this number, and there is a way in which field 3 can be ignored; see NONMEM Users Guide, Part II.

The number of data items per data record is placed in field 4. This number must be between 1 and 20. This does not represent a significant limitation; data records designated as missing DV data items can effectively serve as continuations of data records.

The DATA record in Fig. 2 illustrates the above remarks.

C.3.2.2. Item Record

The main function of the ITEM record is to specify where various data items of interest are found in the data records. This record must appear in a problem specification. Integer format is used.

The index, i.e. the position in the data record, of the ID data item is given in field 1, the index of the DV data item is given in field 2, the index of the MDV data item is given in field 3, and the index of the L2 data item is given in Field 7. Since a DV data item must always be present in the data record, the integer in field 2 must always be at least 1. However, if the records do not include ID data items, a blank or 0 should be placed in field 1, and similarly with respect to fields 3 and 7. The ITEM record in Fig. 2 illustrates these remarks. Since ID, MDV, and L2 data items are not included in the data records, 0's are placed in fields 1, 3, and 7 (a blank acts like a 0).

A blank or 0 should be placed in field 4 unless the INDXS feature is used; this feature is discussed below in section C.4.1.

If the user wants to specify alphanumeric labels to be used in the output for the different types of data items, then a 1 should be placed in field 5. If the user wants NONMEM to specify labels, then a blank or 0 should be placed in field 5. In this case the labels will be VR 1, VR 2, etc. for the first, second, etc. type data items in the data record. The problem specification of Fig. 2 indicates that labels are to be user-specified.

C.3.2.3. LABEL Record

Labels to be used in the tables and scatterplots for the different types of data items are given in the LABEL record. Each label consists of 4 alphanumeric characters, including blanks. The LABEL record is optional. When it appears, labels for *all* the different types of data items must be supplied. When it appears, a 1 must also be placed in field 5 of the ITEM record (see above).

The format of the LABEL record is special; it is unlike any of the formats of the other control records. There are as many fields in the LABEL control record as there are data items in a data record. (However, see NONMEM Users Guide, Part II for a discussion of specifying labels for the NONMEM generated data items.) Each field has four positions, and the label for the ith data item is placed in the ith field. The fields are separated by 4 blanks. See Fig. 2. At most 9 labels can be placed in the fields of a LABEL record comprised of one FORTRAN record, and if there are more than 9 data items per data record, the LABEL record can be continued with other FORTRAN records (9 labels per FORTRAN record).

C.3.2.4. Format Record

The FORTRAN format specification used to read the data items (see section B.1) is supplied in the FORMAT control record. This record must appear in a problem specification (except see the discussion in NONMEM Users Guide, Part II, regarding the first field of the DATA record). The format of the FORMAT record is special; it is unlike any of the formats of the other control records. The specification, including both left and right enclosing parentheses, is placed anywhere in the FORTRAN record immediately following the FORTRAN record containing the preface. See, for example, Fig. 2. This allows the specification to be as long as 80 characters (including left and right enclosing parentheses).

In Fig. 2 the data records follow the FORMAT record, and thus the data set is embedded in the control stream. Embedding the data set in the control stream is always accomplished in this way. In Fig. 2 each data record contains 3 data items. The first data item is the dose amount, the second data item is the time, and the third data item is the DV data item.

C.3.3. Model Specification Records

C.3.3.1. STRUCTURE record

There is just one model specification record needed for a simple nonlinear regression problem, the initial STRUCTURE record. The dimension of the parameter space is obtained from the information given in this control record. Sometimes additional STRUCTURE records are needed in a problem specification. The initial STRUCTURE record is required unless a Model Specification File is input (see section C.4.4). Integer format is used.

There are 8 fields on this record, but only 3 of these are of concern with simple nonlinear regression. The length of THETA is placed in field 1. In the example this number is 3. The number of random interindividual effects is placed in field 2. In the example this number is 1. The only random effect is η, and as explained in section A.5, it is a random interindividual effect. A 1 is placed in field 6. This has the effect of informing NONMEM that the variance-covariance matrix Ω of all random interindividual effects is diagonal. With simple nonlinear regression, where there is only one such effect, Ω is a simple scalar quantity (σ^2), and this is the simplest example of a diagonal matrix.

C.3.4. Initial Estimate Records

C.3.4.1 Introduction

Initial estimates of the model parameters are used in several ways. If a minimization search for parameter estimates is carried out, the search will begin at the initial estimates. When a search is continued from a previous problem, and a Model Specification File is input for this purpose, then the search begins from where it left off in the previous problem. In this case initial estimate records are not required. If a search is not undertaken, tables and scatterplots can still be generated, and the NONMEM generated data items (e.g. prediction, residual, and weighted residual data items) will be computed using the initial estimates (unless, again, a Model Specifcation File is used). An initial estimate should represent the best guess of the population value of the parameter. Some appropriate scale for the parameter should be implied by the initial estimate. The value 0 (a number which has no scale) is never allowed unless the parameter is fixed to this value. Parameters can be fixed in value; this will be described below. There can sometimes be problems in guessing at population values. NONMEM provides some help in this regard. This is illustrated in section C.3.4.6 below and in section C.4.5.

C.3.4.2. THETA CONSTRAINT Record

Control parameters concerned with constraining the elements of THETA are given in the THETA CONSTRAINT record. Constraints on THETA elements are necessary when NONMEM must obtain initial estimates of some of these elements; see section C.4.5. They also may be used for obtaining final

estimates of these elements. In this latter context, the minimization search is undertaken in a constrained parameter space. Each THETA element may be individually constrained (or not) to lie in an interval of the form (a,b), where a may be $-\infty$ and/or b may be ∞. Or perhaps a=b, in which case the element is fixed to the value a. The value a is called the lower bound, and the value b is called the upper bound.

Integer format is used with the THETA CONSTRAINT record. This record is required unless a Model Specifcation File is input. (However, there is the following exception to this rule which should only be of interest to Version II users. The THETA CONSTRAINT record is new to Version III. It is used in part to replace the use of fields 4 and 5 of the initial STRUCTURE record. Field 1 on the THETA CONSTRAINT record is equivalent to field 4 of the INITIAL STRUCTURE record. Field 5 of the INITIAL STRUCTURE record is unnecessary with Version III. Version III ignores fields 4 and 5 *unless* the THETA CONSTRAINT record is missing from the problem specification. Fields 4 and 5 of the initial STRUCTURE record will be deactivated with Version IV.)

If none of the THETA elements are to be constrained, a 0 is placed in field 1. In Fig. 2 a 1 appears in field 1, indicating that some of the THETA elements are to be constrained. There is one other field in this record; it is described in section C.4.5.

C.3.4.3. THETA Record

Initial estimates of the elements of THETA should be placed in the fields of the THETA record. The initial estimate of the ith element is placed in the ith field. Fixed point format is used. This record is required unless a Model Specification File is input.

In the THETA record of Fig. 2 the three initial estimates are 1.7, .102, and 29. These estimates were obtained using the"method of residuals" (sometimes called the "peeling" or "feathering" method) for fitting exponentials, described in Gibaldi and Perrier, 1982, Appendix C.

C.3.4.4. LOWER BOUND Record

If a finite lower bound is to be given for some THETA element, then lower bounds must be given for all THETA elements in the LOWER BOUND record. (Also, in this case upper bounds must be given for all THETA elements in the UPPER BOUND record.) However, any THETA element can be effectively unbounded from below by using the lower bound $-\infty$. These lower bounds should be placed in the fields of the LOWER BOUND record. The lower bound for the ith element is placed in the ith field. A lower bound $-\infty$ is given by the value -1000000. Fixed point format is used. This record is required when and only when there is a THETA CONSTRAINT record with a 1 in field 1. Lower bounds are shown in Fig. 2.

C.3.4.5. UPPER BOUND Record

If a finite upper bound is to be given for some THETA element, then upper bounds must be given for all THETA elements in the UPPER BOUND record. (Also, in this case lower bounds must be given for all THETA elements in the LOWER BOUND record.) However, any THETA element can be effectively unbounded from above by using the upper bound ∞. These upper bounds should be placed in the fields of the UPPER BOUND record. The upper bound for the ith element is placed in the ith field. An upper bound ∞ is given by the value 1000000. Fixed point format is used. This record is required when and only when there is a THETA CONSTRAINT record with a 1 in field 1. Upper bounds are shown in Fig. 2.

C.3.4.6. DIAGONAL Record for Ω

The initial estimates of the elements of the variance-covariance matrix Ω of the random interindividual random effects are given in the DIAGONAL record for Ω. Recall that with simple nonlinear regression Ω is specified to be diagonal (see discussion above about the initial STRUCTURE record). If

Ω is not diagonal, the initial estimates would be given in BLOCK SET records; see section D.5.3. The initial estimate of the ith diagonal element is placed in the ith field of the DIAGONAL record. Fixed point format is used. This record is required whenever there are random interindividual effects, unless a Model Specification File is input.

With simple nonlinear regression $\Omega = \sigma^2$, a simple scalar quantity. Most nonlinear regression programs do not require the user to supply an initial estimate of σ^2; NONMEM is no exception. Whenever the fields of the DIAGONAL record are left blank *and* a 2 is placed in position 8 of this record, NONMEM will try to obtain an initial estimate of Ω using the data. See the DIAGONAL record in Fig. 2.

When initial estimates are user-supplied, then there must be initial estimates for all diagonal elements, i.e. no field can be left blank. An initial estimate of a population interindividual variance component should represent the best guess of this component, and it is best to overestimate the component, rather than underestimate it. The matrix Ω can be fixed to its estimate. This is accomplished by placing a 1 in position 8 of the DIAGONAL record.

Whenever NONMEM is asked to obtain an initial estimate, the Initial Estimate Step is implemented. The printout from this step consists of a display of all the elements of the initial parameter estimate. For the example, see Fig. 4. There the initial estimates of the θ's are given under the heading THETA - VECTOR OF FIXED EFFECTS and are the ones given in the THETA record, and the initial estimate of σ^2 is given under the heading OMEGA - COV MATRIX FOR RANDOM EFFECTS and is 1.17, a number computed by NONMEM.

C.3.5. Task Specification Records

C.3.5.1 ESTIMATION

The Estimation Step is controlled by information given in the ESTIMATION record. When this records is included in a problem specification, the Estimation Step can be executed. When it is absent from the problem specification, the Estimation Step is not implemented. Integer format is used.

A blank or 0 is normally placed in field 1. A 1 can be placed in this field, and then even though the ESTIMATION record appears, the Estimation Step is not implemented, and the remaining fields of the ESTIMATION record may be ignored.

During a minimization search, the objective function must be computed at a number of points in the parameter space, and the number of such evaluations is a measure of the work done during the Estimation Step. The user establishes an upper limit to this number and places this limit in field 2. The search will terminate unsuccessfully if this particular number (or a slightly greater number) of objective function evaluations is attained. In this case a final parameter estimate results which is usually better than the initial estimate, but it is not optimal. The search may be conveniently and smoothly continued in a subsequent NONMEM run, and without starting the search from the beginning and specifying a larger upper limit to the number of function evaluations. This is described in section C.4.4. It requires writing a Model Specification File. In Fig. 2 the number of maximum function evaluations is given as 240.

The minimization search is divided into stages called iterations. At the end of each iteration a parameter estimate results. It is called the iteration estimate. The value of the objective function at the estimate at iteration m is larger than the value of the objective function at the estimate at iteration m+1. The iteration estimate at the 0th iteration is taken to be the initial estimate. The search terminates only when the the two estimates at two successive iterations agree in *at least* the first r significant digits (including leading zeros after the decimal point) with respect to each of the parameter components. Recall that in our simple nonlinear regression example there are four parameter components, θ_1, θ_2, θ_3, and σ^2. The number r is specified by the user and is placed in field 3. In this regard the user should be aware that the minimization search is actually carried out in a reparametrized space established by NONMEM (see below), and, to be precise, the criteria for a successful termination apply to estimates of parameters in this

space. However, usually a reasonable approach to specifying r when, as suggested above, the initial estimates are the user's best guess of the population values of the parameters, is as follows. For each parameter component, let q be the number of significant digits (*excluding* leading zeros after the decimal point) in its initial estimate that the user feels with a fair degree of certainty are accurate. The number q could be zero, of course. Let m be the minimum value of q over all parameter components, and let r be m+2, or m+3. With Double Precision NONMEM, r could be a little larger, m+4 or m+5. If after examining the output, the user feels that the search should be continued using a greater value of r, this may be done conveniently in a subsequent run (see section C.4.4). In Fig. 2 r is set to 4.

The progress of the search may be monitored, and a summary of the progress after every n iterations, starting with the first iteration, will be printed. The number n is placed in field 4. Summaries after the 0th iteration and last iterations are also printed. If no summaries are wanted, a blank or 0 should be placed in field 4. Examples of these summaries are given in Fig. 5, where summaries after every 2 iterations are printed; this output results from the problem specification of Fig. 2.

A summary at the end of an iteration includes the iteration estimate. The estimate is given in terms of a reparametrization established by NONMEM. The new parameters are called the scaled transformed parameters (STP). In a simple nonlinear regression, each of the STP is obtained by transforming and then scaling one of the original parameters. The first several of the STP are obtained in order from the first several θ's, and the last of the STP is obtained from σ^2. Each STP is scaled so that the absolute value of its initial estimate is 0.1 (see the summary of the 0th iteration in Fig. 5).

A summary also includes the value of the objective function evaluated at the iteration estimate. Notice from Fig. 5 that these values decrease from iteration to iteration. A summary also includes the gradient vector of the objective function with respect to the STP and evaluated at the iteration estimate. It can be seen in Fig. 5 that the gradient vector at the last iteration is a several orders of magnitude smaller than that at the 0th iteration. This reflects the fact that the final estimate effectively minimizes the objective function. Lastly, a summary also includes the number of function evaluations computed during the iteration.

Three lines of output are always generated by the Estimation Step in addition to iteration summaries. The first line gives the reason the minimization terminated. In Fig. 5 the reason given is that the criteria for a successful termination were satisfied. Another reason could have been that the maximum number of function evaluations was attained. A third reason could have been that the search algorithm could not conclude that a minimum had been attained due to round-off problems. If the search terminates for either the second or third reasons, the termination is referred to as being unsuccessful. The second line gives the total number of times the objective function was evaluated during the search. The third line gives an estimate of the number of significant digits in the final estimate. This number is a decimal fraction. Let n_1 be the integer part of this number, and let n_2 be the greatest integer that could have been placed in field 3 with the effect that a successful termination would have resulted (there being no upper limit to the number of function evaluations). When the maximum number of function evaluations is not attained, then $n_1 = n_2$. When the maximum number of function evaluations is attained, $n_1 \leq n_2$. When the termination is successful, n_1 is, of course, no less than the integer in field 3. The number of significant digits in the final estimate for the example (see Fig. 5) is 8.5.

When the search terminates unsuccessfully due to problems with rounding errors, this means that changes in the objective surface around the minimum are too small to be distiguished from machine round-off effects. This determination depends on computed information about the surface curvature. There are several possible user-responses. If the number of significant digits in the final estimate is satisfactory, and if the gradients at the minimum are several orders of magnitude smaller than the gradients at the initial estimate, then cautiously ignore the message. If single-precision NONMEM was used, try using double-precision NONMEM. If the initial estimates are within a few percent of previously obtained final estimates which result from a successful termination, then re-run, using initial estimates that are perturbed $\geq$ 10% from these final estimates. One common reason for round-off problems is that

the model is over-parameterized. If the suggested user-responses given above neither apply nor help, then the user should consider a model with fewer parameters.

The iteration summaries can be useful in a few ways. First, one can use them to check that the search indeed converged to a local extremum of the objective function surface, by checking that the gradients are relatively small. It is possible for the message that the search terminated successfully to be issued while the search, in fact, did not converge to a local extremum, let alone a local minimum. Second, one can use them to check that some mistake has not been made or that the model is not extremely overparameterized, by checking that the parameter estimate changes during the search. This, of course can also be done by comparing the final parameter estimate to the initial parameter estimate, but this is easy to check at a glance from the iteration summaries. Sometimes a coding error in a user-supplied routine results in a parameter not having any influence on the fit, in which case its estimate will not change during the search. If the model is extremely overparameterized, this too may result in no change in some parameter estimate. Sometimes the search will extend into a region of the parameter space where numerical difficulties will occur and error messages reflecting these difficulties will be output. If these messages are intermingled in the earlier iteration summaries, but do not appear in the later summaries, and if the final parameter estimate is reasonable, one may conclude that the search returned to a more reasonable and less problematic area of the parameter space before terminating.

Lastly, there can be indication with the 0th and early iteration summaries that some mistake has been made. If at the 0th iteration, the gradient vector is zero, this could indicate that numerical constants have not been set appropriately in NONMEM itself at installation time (see Users System Guide) or that double precision NONMEM is being used while double precision is not being handled correctly in a user-supplied subroutine. In the latter case, often a user forgets to declare some variable (depending on a θ) as a double precision variable. When the value of the objective function at the 0th iteration estimate is an extremely large (usually the largest floating point number representable on the machine), and the gradient vector is also zero, this usually indicates that there has been a mistake in either user-supplied code, the data, or the initial estimates. In particular, the user should check these three things for mistakes that could affect partial derivatives since the symptomology in question results when the variance-covariance matrix of the data from some individual is initially estimated to be singular.

Whether or not the Estimation Step is implemented, the final parameter estimate is printed. In the latter case, the final estimate is taken to be the initial estimate. Fig. 7 shows the final estimate for the example. The number .899, appearing under the heading OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS, is the final estimate of σ^2. The minimum value M of the objective function is also printed. Fig. 6 shows this minimum value for the example. With simple nonlinear regression, and using the ELS objective function, M coincides (except for a parameter-independent additive constant) with -2L, where L is the logarithm of the likelihood of the data evaluated at the maximum likelihood parameter estimate, *under the assumption* that the η_i are normally distributed. The minimum value may be used across runs to develop likelihood ratio type tests of hypothesis about the parameters (Gallant, 1975).

C.3.5.2. COVARIANCE Record

The Covariance Step is controlled by information given in the COVARIANCE record. When this record is included in a problem specification, the Covariance Step can be implemented. When it is absent from the problem specification, the Covariance Step is not implemented. This may be done when, for example, the user is focusing on the Estimation Step only. The Covariance Step may be implemented in a subsequent run without repeating the Estimation Step (see section C.4.4). It is an error to include the COVARIANCE record when the Estimation Step is not implemented and a Model Specification File is not input. This is because the validity of the covariance matrix depends heavily on the condition that the parameter estimate minimize the objective function, and NONMEM wants to be assured that such an estimate is available. Integer format is used.

A blank or 0 is normally placed in field 1. This means that the Covariance Step is conditionally implemented, i.e. it is implemented only if the Estimation Step terminates successfully. However, this condition can be over-ridden by placing a 1 in field 1. Then regardless whether the Estimation Step terminates successfully, the Covariance Step is also implemented. Also, a 2 can be placed in field 1, and then even though the COVARIANCE record appears, the Covariance Step is not implemented, and the remaining fields of the COVARIANCE record may be ignored.

There are other fields in the COVARIANCE record, most of which are described in NONMEM Users Guide, Part II. Field 5 is discussed below; this discussion is relevant only when the computation implemented in PRED is recursive.

Implementation of the Covariance Step results in a printout of the estimates of the standard errors of the parameter estimates, the covariance matrix, the inverse of the covariance matrix, and the correlation form of the covariance matrix. The reader is reminded that the standard error estimates are the square roots of the diagonal elements of the covariance matrix. Fig. 8 shows the standard error estimates for the example. The number .545, appearing under the heading OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS, is the standard error estimate for $\hat{\sigma}^2$. Fig. 9 shows the full covariance matrix. The label OM11 refers to $\hat{\sigma}^2$. The covariance of $\hat{\sigma}^2$ with any one of the $\hat{\theta}'$s is not zero, reflecting the fact that for the purpose of computing the covariance matrix, the random errors in the models (the η_i) are not assumed to be normally distributed.

The user should be familiar with the covariance matrix associated with use of the least squares objective function. The computation of this matrix does not rest on a normality assumption about the η_i (Jennrich, 1969), although the computation can also be justified under the assumption that the η_i are normal, using maximum likelihood theory (Hoadley, 1971). Similarly, the covariance matrix associated with use of the extended least squares objective function does not rest on a normality assumption (Beal, 1984b). This covariance matrix includes the variance of $\hat{\sigma}^2$ and the covariances of $\hat{\sigma}^2$ with the $\hat{\theta}'$s. Under the normality assumption, a similar covariance matrix can be computed, one, however, where these covariances are always zero.

Fig. 10 shows the correlation matrix, and Fig. 11 shows the inverse of the covariance matrix.

Field 5 of the COVARIANCE record is concerned with PRED routines which are recursive. Another PRED which implements the very same example and produces virtually the same output is given in Fig. 19. It is an example of a recursive PRED, i.e. the value of the argument F returned with a given data record depends on computations taking place in PRED with previous data records. The computation is based on the superimposition principle with linear kinetic systems which in this case allows the regression function for the ith observation to be written recursively as

$$f(\theta_1, \theta_2, \theta_3, x_{1i}, x_{2i}) = B(\theta_1, \theta_2, \theta_3, d_{i-1}, x_{2i} - x_{2i-1}) + f(\theta_1, \theta_2, \theta_3, x_{1i}, x_{2i-1}) \exp(-\theta_2(x_{2i} - x_{2i-1}))$$

where

$$B(\theta_1, \theta_2, \theta_3, d, \delta) = \frac{\theta_1 d}{\theta_3(\theta_1 - \theta_2)} (\exp(-\theta_2\delta) - \exp(-\theta_1\delta))$$

$$d_i = d_{i-1} \exp(-\theta_1(x_{2i} - x_{2i-1}))$$

where the initial conditions are

$$f(\theta_1, \theta_2, \theta_3, x_{10}, x_{20}) = 0$$

$$x_{20} = 0$$

$$d_0 = x_{11}$$

and where the time points x_{2i} are ordered from low to high values, and the dose amounts x_{1i} are constant. The function B is the Bateman function. PRED calls the subroutine BATE which computes this function. The code for BATE is given in Fig. 20.

For the purpose of computing the covariance matrix, a burst of an individual record (see section C.2) can occur immediately after another burst of the same individual record. When both (i) a recursive PRED is used, *and (ii)* the recursion extends across individual records, this pattern of bursts will cause a problem. When conditions i and ii hold, then for PRED to work correctly, a burst of an individual record must be immediately preceeded by bursts of the preceeding individual records, and these bursts must occur in the order in which the individual records appear in the data set. By placing a 1 in field 5 of the COVARIANCE record, NONMEM will only use this more appropriate pattern of bursting. (When either i or ii does not hold, it is far more efficient, but not necessary, to place a blank or 0 in field 5). So the rule is: whenever a recursive PRED is used, *and* when the recursion extends across individual records, a 1 should be placed in field 5, indicating that the computation of the covariance matrix should be done in a special way. The SPECIAL COMPUTATION referred to in the middle of Fig. 3 is this computation. In Fig. 3 it is stated that the special computation is not performed. This is because a blank is placed in field 5 of the COVARIANCE record of Fig. 2. Recall that in the example each data record is an individual record. Therefore, if the recursive PRED were used, a 1 should be placed in field 5, and then the problem summary will state that the special computation is performed.

There is another aspect of the PRED in Fig. 19 which should be noted. In order to initialize the recursion the routine must be made aware of which data record being passed is the first data record of the data set The argument NEWIND has the value 0 only when the data record being passed is this first data record. The other values it can have are 1 and 2. When the record is the first record of an individual record, the value of NEWIND is 1 (except with the first individual record, where this value is 0). When the record is the second or subsequent record of an individual record, the value of NEWIND is 2.

C.3.5.3. TABLE Records

The Table Step is controlled by information given in the TABLE records. When these records are included in the problem specification, the Table Step can be implemented. The records consist of an initial TABLE record followed by one or more individual TABLE records. When they are absent from the problem specification, the Table Step is not implemented. Integer format is used.

A blank or 0 is normally placed in field 1 of the initial TABLE record. This means that the Table Step is conditionally implemented, i.e. it is implemented only if the Estimation Step terminates successfully. However, this condition can be over-ridden by placing a 1 in field 1. Then regardless whether the Estimation Step terminates successfully, the Table Step is also implemented. Also, a 2 can be placed in field 1, and then even though the initial TABLE record appears, the Table Step is not implemented, and the remaining fields of this record may be ignored. Also, in this case no individual TABLE records should appear.

The number of tables to be generated is placed in field 2 of the initial TABLE record. Each table is defined by an individual TABLE record, and the tables will appear in the printout in the same order as that in which their defining individual TABLE records appear.

The tables can be printed, or stored in a Table File, or both. If they are only to be printed, a blank or 0 is placed in field 3 of the initial TABLE record. If they are only to be stored in a Table File, a 1 is placed in field 3, and if they are both to be printed and stored, a 2 is placed in field 3. When they are stored, they are stored one after the other in the Table File, which is a sequential file. The records of this file are exactly the records that appear in the output file when the tables are printed (except that the FORTRAN carriage control characters are not included).

A table is a tabulation of the data items of selected type. The rows of the table correspond to data records, and the columns of the table correspond to the selected data item types. The number of data

item types selected to appear in a table is placed in field 1 of the defining TABLE record. This number must be between 0 and 8. The total number of columns of the table actually equals this number plus 4, because with each table an additional 4 columns are appended by NONMEM. These 4 columns correspond to the DV data item type and the 3 NONMEM generated data item types (see section A.4). Consequently, the user need not select the DV data item type to appear in a table. When the NONMEM generated data items types are the prediction, residual, and weighted residual, then 0 is tabulated for residual and weighted residual data items with data records designated as missing.

In the example corresponding to Fig. 2 only one table is to be generated; it is to be printed only. There is only one data item type selected for tabulation, the time data item type. Fig. 13 shows this table. Note that since the default objective function is used, the three NONMEM generated data items that appear in the table are the prediction, residual, and weighted residual data items. (In this example, where the statistical error model is homoscedastic, the weighted residual data item is the residual data item divided by the final estimate of σ, the positive square root of the final estimate of σ^2.) These are labeled PRED, RES, and WRES. These labels can be changed, as can the computation of the NONMEM generated data items themselves (see NONMEM Users Guide, Part II).

After the first field of an individual TABLE record, there follow two fields for each selected data item type. The index of the data items of given type is placed in the first of these two fields, and a sort code is placed in the second field. Use of these sort codes to sort the rows of the table on the data items of selected types is described in section D.5.4. Blanks or 0's should be placed in sort fields unless a sort is desired. In this case the column order of the selected data item types corresponds to the order in which the indices of the data items are placed in the TABLE record.

Example C.3.5.3.i:

TABL	3	3	2	7
column no.:	1	1	2	3
	2	6	4	2

In this example three types of data items are selected for tabulation. The first column of the table consists of the data items whose index is 3, the second column consists of the data items whose index is 2, and the third column consists of the data items whose index is 7.

There is a limitation of 900 rows per table. If the number of data records, n, exceeds this limit, any one table will not use all the data records. However, all data records are used in the following way. Each individual TABLE record actually defines a number of tables. A first table is generated which uses data records 1 through min $(n, 900)$. If n > 900, then a second table is generated which uses data records 901 through min $(n, 1800)$. And so on.

C.3.5.4. SCATTERPLOT Record(s)

The Scatterplot Step is controlled by information given in the SCATTERPLOT records. When these records are included in the problem specification, the Scatterplot Step can be implemented. The records consist of an initial SCATTERPLOT record followed by one or more individual SCATTERPLOT records. When they are absent from the problem specification, the Scatterplot Step is not implemented. Integer format is used.

A blank or 0 is normally placed in field 1 of the initial SCATTERPLOT record. This means that the Scatterplot Step is conditionally implemented, i.e. it is implemented only if the Estimation Step terminates successfully. However, this condition can be over-ridden by placing a 1 in field 1. Then regardless whether the Estimation Step terminates successfully, the Scatterplot Step is also implemented. Also, a 2 can be placed in field 1, and then even though the initial SCATTERPLOT record appears, the SCATTERPLOT Step is not implemented, and the remaining fields of this record may be ignored. Also, in this case no individual SCATTERPLOT records should appear.

Families of scatterplots are generated. The number of families to be generated is placed in field 2 of the initial SCATTERPLOT record. Each family is defined by an individual SCATTERPLOT record, and the families will appear in the printout in the same order as that in which their defining individual SCATTERPLOT records appear.

The simplest kind of a family consists of a single scatterplot of two types of data items, one for use along the abscissa axis and one for use along the ordinate axis. Examples of these families are shown in Figs. 15-18. These families are defined by the individual SCATTERPLOT records of Fig. 2. The first family consists of the plot of the DV data items vs the time data items. The second family consists of the plot of the prediction data items vs the time data items. The third family consists of the scatterplot of the residual data items vs the time data items. Whenever residuals or weighted residuals are plotted, the "zero line" is also shown. The fourth family consists of the scatterplot of the prediction data items vs the DV data items. Note that in this scatterplot the line with slope equal to 1 is shown. This line is called the unit slope line, and it can be optionally included in any scatterplot. Also, notice that the axes on which the predictions and residual data items are plotted are labeled PRED and RES, respectively. The labels used in the scatterplots are the same ones used in the tables (see section C.3.5.5). More complicated families than those illustrated in Figs. 15-18 are described in section D.5.5.

In each individual SCATTERPLOT record the index of the data items to be plotted on the abscissa axis is placed in field 1, and the index of the data items to be plotted on the ordinate axis is placed in field 2. For the purpose of defining scatterplots, the indices of the NONMEM generated data items are n+1, n+2, and n+3, where n is the number of data items per data record as specified in the DATA record. If the unit slope line is wanted with the scatterplots of a particular family, then a 1 is placed in field 6; otherwise a blank or 0 is placed in the field.

C.4. Additional Features

C.4.1. INDXS

In the PRED in Fig. 1 the positions of the dose and time data items in the data records are assumed to be 1 and 2, respectively. It would be convenient to have a code which is independent of an assumption about the positions of data items in the data records. Such a code is given in Fig. 21. It will work with the data set embedded in the control stream of Fig. 22, which is just like the data set embedded in the control stream shown in Fig. 2. It will also work with the data set emdedded in the control stream shown in Fig. 23 which is just like that embedded in the control stream of Fig. 2 except that the positions of the dose and time data items are reversed. The code employs an indirect addressing feature. Suppose, as in the example, two data items are needed in the computation, and in the code they are numbered 1 and 2 (1 - dose; 2 - time). The position of the Ith such data item in the data record is given by INDXS(I), where INDXS is a one-dimensional array appearing in the argument list to PRED. For example, for PRED to work correctly with the data set shown in Fig. 23, INDXS(2) must equal 1.

The user sets the appropriate values in INDXS by placing the Ith value in the Ith field of the INDEX record. Integer format is used for the INDEX record. This record is optional, but if the indirect addressing feature is used in PRED, then it should appear in the problem specification. It can actually be used for the more general purpose of communicating integer-valued numbers to PRED. When it used, it is placed after the ITEM record in the problem specification. In this case the number of indices occuring in the INDEX record is placed in field 4 of the ITEM record. These remarks are illustrated in both Figs. 22 and 23.

C.4.2. ICALL

Since in the example dose is a constant, the dose need not be given on any data record. Rather, the dose could be obtained by PRED itself during an initial stage, and thereafter be available in PRED's local storage. Indeed, there exist PRED initializations, special calls to PRED during which PRED computa-

tions can be initialized; At a PRED initialization the routine is not expected to return values in F and G. PRED must be able to recognize these special calls. The first argument to PRED is ICALL. At a PRED initialization ICALL has the value 0 or 1. When PRED must return values in F and G, ICALL has the value 2. At a PRED initialization the values in THETA are the initial estimates (or if an initial estimate of some θ is not given, then the midpoint between the lower and upper bounds is used), and the data record passed in DATREC is the first data record. So even though the call is a PRED initialization and PRED is not checking ICALL, usually no difficulty is encountered when PRED proceeds to compute F (see Fig. 1).

A PRED that checks ICALL is shown in Fig. 24. At ICALL=1, the dose is read by PRED on FORTRAN unit 5. Unit 5 is the unit connected to the file containing the control stream. With a control stream containing just one problem specification the entire control stream is read by NONMEM before a PRED initialization, so no difficulty arises by including records in this file after the control stream which are to be read by PRED. The sequence of records in the file might look like that shown in Fig. 25 which consists of a control stream followed by a record to be read by PRED and containing the dose. Of course, the "dose record" could also be in a file connected to a different FORTRAN unit from 5. The control stream in Fig. 25 is just like that of Fig. 2, but it is adjusted for the absence of dose in the data records.

There are a number of PRED initializations. The first one occurs at the beginning of the NONMEM run and allows PRED computations to be initialized over all problems. This is signalled to PRED with ICALL=0. The other PRED initializations follow, one occuring at the beginning of each problem. These are signalled to PRED with ICALL=1. Since in the example there is only one problem, at ICALL=0 PRED simply returns control to NONMEM, waiting for ICALL=1 at which time the problem is initialized by obtaining the dose.

At a PRED initialization (all) the data can also be transgenerated. See NONMEM Users Guide, Part II.

There also exist PRED finalizations, special calls to PRED enabling computations in the routine to be finalized. Such computations could produce output not generated by NONMEM itself. There is one PRED finalization at the end of each problem. These calls are signalled to PRED with ICALL=3. At a PRED finalization the first data record of the data set is passed in DATREC, but the values in THETA are the final estimates. Therefore, one can, for example, compute and output the maximum value of the regression function with respect to time, i.e.

$$\frac{\text{dose}}{\theta_3}\ \exp\ (-\frac{\theta_2}{\theta_1-\theta_3})\ \log\ (\frac{\theta_1}{\theta_2})$$

evaluated at θ equal to its final estimate. Printed output from PRED may be placed in the same file as that containing NONMEM output, the file connected to unit 6. However, this may not be satisfactory since such printout follows the problem summary and preceeds the printout from the Estimation, Covariance, Tables, and Scatterplot steps. If this is done, then a page skip should begin this printout. During a PRED finalization, the data can also be transgenerated, and the transgenerated data are then available for tables and scatterplots.

C.4.3. Using the MDV Data Item

The idea of including additional data records with only dummy DV data items to "fill out" a plot of prediction vs an independent variable (e.g. time) has been mentioned in section B.1. Some elaboration of that discussion and an illustration is given in this section.

Examination of the plot of prediction vs time given in Fig. 16 shows that the curve has a "gap" between 12 and 24 hours. The control stream in Fig. 26 is very similar to that of Fig. 2, but the data includes data records with time data items 16 and 20 hours, so that the plot of prediction vs time has less

of a gap. The plot is shown in Fig. 27. None of the other plots are affected by the presence of the two new data records since data records designated as missing are not used with scatterplots involving the DV, residual, or weighted residual data items. Also, the output from the Estimation and Covariance steps is not affected by the presence of the two new data records. The table simply has two additional rows in which the residual and weighted residual data items are 0.

There are other differences between Figs. 2 and 26. First, MDV data items are included. The MDV data item is 1 in the records with times 16 and 20, indicating that these two records are designated as missing DV data items. Actually, dummy data DV data items exist in these two records (the number 0, since for convenience and perspicuity, blanks are used, and blanks translate to 0). Second, ID data items also are included since *whenever* MDV data items exist, so must ID data items. The ID data item 9 is used in each of the two additional data records. However, any ID data items whatsoever could have been used in these two records, and the computation would not have been affected. Third, the presence of both ID and MDV data items is indictated in the ITEM record. Fourth, other minor changes occur since now there are 5 data items per data record altogether; see, for example, the SCATTERPLOT records.

C.4.4. Model Specification File

The minimization search implemented in the Estimation Step will terminate either successfully or unsuccessfully. In either case the last iteration estimate may be placed in an output file. The information in the model specification records is also recorded in the file. Therefore, the file is called the Model Specification File (MSF). This file is useful when, for example, the user wishes to proceed cautiously with a large and possibly difficult minimization search and not allow the search to proceed too far before reviewing the results. This can be done by setting the maxmum number of function evaluations to an appropriately small number. Then if the results are encouraging, the search can be continued in a second problem in a subsequent NONMEM run. Since the MSF contains the model specification and initial estimate information that is needed in this second run (the initial estimate would now be the last iteration estimate of the first problem), it can be input in the second problem, and the model specification and initial estimate records need not be included. However, the benefit in using an MSF is greater than that in just allowing certain control records to be omitted. The MSF also contains useful information about the curvature of the objective function in the area of the last iteration estimate. This allows a search which is continued using the MSF to proceed in an informed and efficient manner, just as if it were not aborted in the first problem. This is referred to as a smooth continuation. This is in contrast to what would happen if the user were to specify the last iteration estimate of the first problem in the initial estimate records of the second problem. In this case the search proceeds less efficiently since information about the curvature of the objective function is not available and must be freshly obtained. Indeed, if the last iteration estimate of the first problem is nearly optimal, the search could terminate due to rounding errors.

The benefit in using an MSF becomes even greater in another situation. Suupose the user chooses a number of maximum function evaluations which is so large that it seems that it would not be attained, but in fact, it is attained. In this event the search would need to be repeated, or at least continued. It would be unfortunate if the search were expensive in terms of time and/or money. With a MSF, it could be easily and smoothly continued.

Or to take yet another example, the user may wish to first examine the results of the Estimation Step, even if it terminates successfully, before implementing the Covariance Step. Since the computation in the Covariance Step depends heavily on the final estimate minimizing the objective function, then when the Estimation Step is not implemented, NONMEM does not even allow the Covariance Step to be implemented *unless* an MSF is input.

Another control stream is given in Fig. 28. This one differs from that in Fig. 2 in just a few respects. First, the maximum number of function evaluations, as given in the ESTIMATION record is 50. Since the search is known to use 114 function evaluations (see Fig. 5), use of this control stream results in an unsuccessful termination of the search due to the maximum number of function evaluations

being exceeded. This is indicated by the output from the Estimation Step shown in Fig. 30. Second, a 1 is placed in field 6 of the ESTIMATION record, indicating that a MSF is to be output. (Field 5 is described in NONMEM Users Guide, Part II.) When field 6 contains a blank or 0, then a MSF is not output. Lastly, a file name in the FILE record is given since a nonnull file stream must be specified (see section B.3). This name is: FILESTREAM. The records in the file FILESTREAM are shown in Fig. 29. They consist of the MODEL SPECIFICATION FILE OUTPUT record, giving the name (MSF1) of the Model Specification File, and the problem delimiter record.

From the progress of the search, as indicated in Fig. 30, there is little reason to think that successful termination would not have resulted had the maximum number of function evaluations been considerably greater than 50. A run using the MSF as an input file is therefore undertaken. A control stream for this run is given in Fig. 31. This control stream also differs from that in Fig. 2 in just a few respects. First, the model specification and initial estimate records of Fig. 2 are replaced by a new model specification record, the FIND record. The FIND record informs NONMEM that a MSF is input. For most purposes, the fields of this record can be ignored (for details though, see NONMEM Users Guide, Part II). Second, the maximum number of function evaluations is now 150. Third, a 1 is once again placed in field 6 of the ESTIMATION record, indicating that another MSF is to be output from this second problem. Fourth, again, a file name is given in the FILE record. Fig. 32 shows the records in FILESTREAM for this problem. They consist of the MODEL SPECIFICATION FILE OUTPUT record, the MODEL SPECIFICATION FILE INPUT record (the order here is necessary; see section B.3), and the problem delimiter record. The iteration summaries resulting from this problem are given in Fig. 33. Notice that they can be attached to the iteration summaries resulting from the first problem (Fig. 30), and together they give the summaries shown in Fig. 5.

C.4.5. Initial Estimates for θ

In the example perhaps that element of θ for which it is most difficult to obtain an initial estimate is θ_1, the rate constant for absorption. Fig. 34 shows a control stream exactly like that in Fig. 2 except that the initial estimate for this parameter is left blank. Whenever any initial estimate is left blank, the Initial Estimate Step is implemented, and NONMEM tries to obtain the initial estimate. Any number of initial estimates may be left blank. The output from the Initial Estimate Step for this control stream is given in Fig. 35. There an initial estimate for θ_1 is given as 1.5. The output from the other steps is essentially like that for the control stream in Fig. 2.

In order to obtain an initial estimate for an element of θ the user must supply finite lower and upper bounds for the element. These bounds, over all elements for which NONMEM must obtain initial estimates, form a "rectangular" parameter space, and a number of points, n, in this space are examined in succession. The initial estimates are obtained from that point giving the lowest value of the objective function. (An initial estimate for σ^2, or for any other variance-covariance component in the model which is not specified by the user, is determined by a given value for θ.) There is a default value for the number n which is taken to be 10% of an estimate of the number of objective function evaluations that will be necessary to minimize the objective function in the Estimation Step. This default may be overridden. The desired value for n may be placed in field 2 of the THETA CONSTRAINT record.

D. Nonlinear Regression with Nonnested Random Effects

D.1. Introduction

In this chapter the example discussed in chapter C is elaborated in order to begin illustrating the large variety of modeling possibilities using NONMEM.

The statistical model considered in chapter C has exactly one random effect. As such, it is a particular example of a class of regression models with possibly more than one random effect and where no random effect is nested within any of the others. An example of such a model, again a nonlinear regression model with just one random effect, but which does not have the simple error structure of the example of chapter C, is discussed in sections D.2 and D.3. Another example with two random effects is discussed in sections D.4 and D.5.

D.2. Example with One Random Effect

In recent years a variant of the statistical model discussed in chapter C has been found useful in kinetic situations. Let $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$, and let

$$y_i = f_i(\theta) + g_i(\theta)\eta_i$$

where

$$f_i(\theta) = f(\theta_1, \theta_2, \theta_3, x_{1i}, x_{2i})$$

$$g_i(\theta) = f(\theta_1, \theta_2, \theta_3, x_{1i}, x_{2i})^{\theta_4}$$

and f is as in chapter C. Again, there is only one random effect, η, whose values for the observations in the data set, the η_i, are statistically independent random errors with means 0 and commmon variance σ^2. However, with this model

$$\text{var}\,(y_i) = \sigma^2 f_i(\theta)^{2\theta_4},$$

i.e. the variances of the y_i are proportional to an (unknown) power of the mean values of the y_i. If $\theta_4 = 0$, the model reduces to the simple nonlinear regression model. If $\theta_4 = 1$, the coefficient of variation of the y_i is constant across i, viz. σ. In order to implement this model it is important to note that in the expression for this model the random effect occurs linearly and that its coefficient is a value of a function g evaluated at θ; see section D.3.

The ELS objective function with this model is:

$$O(\theta, \sigma^2) = n \log \sigma^2 g_i(\theta)^2 + \sum_{i=1}^{n} (y_i - f_i(\theta))^2/(\sigma^2 g_i(\theta)^2)$$

The efficacy of using this objective function with this model is discussed in Sheiner and Beal, 1985 and Beal and Sheiner, 1988. The objective function can also be written

$$O(\theta, \sigma^2) = n \log \sigma^2 g_i(\theta)^2 + \sum_{i=1}^{n} \left[(y_i - f_i(\theta))/(\sigma g_i(\theta))\right]^2$$

The quantity in square brackets being squared is the weighted residual from y_i, the residual divided by its standard deviation. The weighted residuals are defined as the weighted residuals from all observations y_i.

D.3. Implementation of Example 1

A code for PRED which implements the example is given in Fig. 36. The only difference between this code and the code in Fig. 1 is the value that is returned in G(1). In the earlier code, the value is uniformly equal to 1. In this code the value $g_i(\theta)$ is returned. (This value is uniformly equal to 1 only when

θ_4 is fixed to 0.) In general, the Ith linear coefficient of the Ith random interindividual effect is returned in G(I). Here, though, there is only one random interindividual effect in the model.

A control stream for this example is given in Fig. 37. The essential difference between it and the one in Fig. 2 is that it specifies that there are 4 θ's, rather than 3. The initial estimate of θ_4 is unspecified, but is constrained to be between 0 and 3 (see section C.4.5). Also, this control stream specifies that a plot of weighted residual vs time be obtained, rather than specify that a plot of residual vs time be obtained.

The minimum value of the objective function is computed to be 8.778, not really different from that obtained with the simple nonlinear regression, 8.940. The final estimates of the parameters of the regression function are also only a little different: $\theta_1 = 1.87$ (vs 1.94), $\theta_2 = .105$ (vs .102), $\theta_3 = 31.7$ (vs 32). The estimate of θ_4 is .45, so that the variances of the y_i are estimated to be approximately proportional to the f_i. However, the imprecision in this estimate is large (the standard error estimate is about 400% of the point estimate), and the presence of this parameter in the model is only to provide robustness in the presence of possible heteroscedasticity (Beal and Sheiner, 1988). The plot of weighted residual vs time is also very similar to the earlier plot of residual vs time.

D.4. Example with Two Random Effects

This example is very similar to the one given in chapter C. An oral dose of theophylline is administered to a single subject, but at various times both plasma *and* saliva concentrations are measured. At some times only plasma concentration or only saliva concentrations are measured. Therefore, there will be two types of observations in the data set. The regression function for the plasma concentrations is taken to be the "one-compartment model without absorption"

$$f_p(\theta_2, \theta_3, x_1, x_2) = \frac{x_1}{\theta_3} \exp(-\theta_2 x_2)$$

because although an oral dose was administered, the observations were taken after the absorption phase of the process was effectively over, and only an exponential elimination phase was in progress. The regression function for the saliva concentrations is taken to be

$$f_s(\theta_1, \theta_2, \theta_3, x_1 x_2) = \theta_1 f_p(\theta_2, \theta_3, x_1 x_2)$$

That is, the predicted saliva concentration is modeled to be proportional to the predicted plasma concentration. These two models can be combined into a single regression function as follows.

$$f(\theta_1, \theta_2, \theta_3, x_1, x_2, x_3) = f_p(\theta_2, \theta_3, x_1, x_2) \quad \text{if } x_3 = 0$$

$$\theta_1 f_p(\theta_2, \theta_3, x_1, x_2) \quad \text{if } x_3 = 1$$

where x_3 is the plasma-saliva indicator variable (it has the value 0 if the observation is a plasma concentration, and the value 1 if the observation is a saliva concentration).

In the statistical model the observations are doubly subscripted: y_{ij} is the jth observation from the ith time point. When both plasma and saliva are measured, j assumes the values 1 and 2. When only plasma or only saliva is measured, j assumes the value 1. The statistical model is given by

$$y_{ij} = f(\theta_1, \theta_2, \theta_3, x_{1ij}, x_{2ij}, x_{3ij}) + (1 - x_{3ij})\eta_{1i} + x_{3ij}\eta_{2i}$$

where x_{1ij}, x_{2ij}, and x_{3ij} are values of the independent variables associated with y_{ij}, and the (η_{1i}, η_{2i}) are statistically independent random error vectors with 0 means and common variance-covariance matrix Ω. This 2×2 matrix is another model parameter to be estimated. It contains two possibly different variance components, one corresponding to plasma concentrations and one corresponding to saliva concentrations, since each type of concentration is measured with a possibly different scale. It also contains a covariance component since we wish to account for the possibility that when the two types of concentrations are

measured at the same time point, these measurements (after adjustment for the fixed effects of time and dose) may be statistically correlated. Under the model, when both the observations y_{i1} and y_{i2} are present at the ith time point, since one of them is affected by η_{1i} and the other is affected by η_{2i}, and since these random effects can covary, so then can the two observations. The two observations together, (y_{i1}, y_{i2}), therefore, form a multivariate observation. We let y_i denote the column form of this vector. When only one observation is present at the ith time point, then y_i denotes this single number. There is no nesting of the two random effects. Therefore, they both are treated as random interindividual effects, and as with simple nonlinear regression, the observation vectors y_i are regarded as coming from different individuals (see section A.5).

The model can be rewritten

$$y_{ij} = f_{ij}(\theta) + g_{1ij}\eta_{1i} + g_{2ij}\eta_{2i}$$

where

$$f_{ij}(\theta) = f(\theta_1, \theta_2, \theta_3, x_{1ij}, x_{2ij}, x_{3ij})$$

$$g_{1ij} = 1 - x_{3ij}$$

$$g_{2ij} = x_{3ij}$$

This linear expression in the η's, where the coefficients are given as g's, is similar to the way the model of section D.2 is expressed, and it is called the NONMEM linear model schematic. The term 'linear' here refers to linearly occuring random effects and not to linearly ocurring parameters. By virtue of the observation vector being multivariate at some time points, this model is a type of multivariate nonlinear regression. The absence of a plasma or saliva measurement at some time point makes the situation unbalanced, or from another point of view, there are missing data.

Let I denote the number of time points. Also, for fixed i, let f_i denote the column vector of values of the f_{ij}, let g_{1i} denote the column vector of values of the g_{1ij}, and let g_{2i} denote the column vector of values of the g_{2ij}. The ELS objective function is given by

$$O(\theta, \Omega) = \sum_{i=1}^{I} \left[\log \det C_i(\Omega) + R_i(\theta, \Omega)' R_i(\theta, \Omega) \right]$$

where

$$R_i(\theta, \Omega) = C_i(\Omega)^{-1/2}(y_i - f_i(\theta))$$

$$C_i(\Omega) = g_i \Omega g_i'$$

$$g_i = (g_{1i}, g_{2i})$$

The matrix C_i is the variance-covariance matrix of y_i. The vector R_i is the vector of weighted residuals from the observations y_i. As with the previous example, it has the form residual (vector) divided by standard deviation (matrix), and it is "squared" in the expression for the objective function. The weighted residuals are defined to be the weighted residuals from all obervations y_i.

D.5. Implementation of Example 2

D.5.1. Introduction

A code for PRED which implements the example is given in Fig. 38. Note that the values $g_{1ij}(\theta)$ and $g_{2ij}(\theta)$ are returned in G(1) and G(2), respectively. As with the previous example, these are the

coefficients of η_{1i} and η_{2i} in the NONMEM linear model schematic. In general, the value returned in G(I) is the coefficient of the Ith random interindividual effect in the NONMEM linear model schematic.

A control stream for this example is given in Fig. 39. The data set is embedded in it, and like the data of the previous example, the first, second, and third data items in a data record are the dose, time, and DV data items, respectively. However, there is also a fourth type of data item, the plasma-saliva indicator data item. This is labeled P/S. The DV data item is either a plasma concentration or a saliva concentration, according as the P/S data item is 0 or 1, respectively. Since all observation vectors are regarded as arising from different individuals (see section D.4), and since some observation vectors contain two elements, a plasma and a saliva concentration, ID data items must be present in the data records. These will assure that both elements are identified with the same individual. Since the individual changes as time changes, the time data item has been chosen to serve as the ID data item. Therefore, a 2 appears in field 1 of the ITEM record. A separate fifth type of data item could have been used for the ID data item.

The control stream contains a new model specification record, the STRUCTURE record for Ω, which is discussed in section D.5.2. It also contains a new initial estimate record, the BLOCK SET record for Ω which is discussed in section D.5.3. Also, sort codes appear for the first time in the TABLE record, and separators appear for the first time in the SCATTERPLOT records. These are discussed in sections D.5.4 and D.5.5. Selected printout which results from using the PRED and the control stream given in Figs. 38 and 39, respectively, is discussed in section D.5.6.

D.5.2. STRUCTURE Record for Ω

There are two STRUCTURE records in Fig. 39, the initial STRUCTURE record and the STRUCTURE record for Ω. Regarding the first of these, since there are now 2 random interindividual effects, a 2 is placed in field 2. The matrix Ω could be constrained to be diagonal, in which case a 1 is again placed in field 6. However, for the sake of this example, no such constraint is wanted. Therefore, instead, a 1 is placed in field 7. This signals that Ω is to be regarded as a full matrix. Another option is to regard Ω as a block diagonal matrix, in which case yet another value is placed in field 7; see NONMEM Users Guide, Part II.

When a 1 is placed in field 7 of the initial STRUCTURE record, i.e. when Ω is not constrained to be diagonal, the most number of random interindividual effects there can be is 5.

When a 1 is placed in field 7 of the initial STRUCTURE record, the STRUCTURE record for Ω must appear after the initial STRUCTURE record. Integer format is used. When a 1, in particular, is placed in field 7 of the initial STRUCTURE record, a 1 is placed in field 1 of the STRUCTURE record for Ω, and the number of random interindividual random effects is placed in field 2. The information in this record is redundant in this example; it is already given in the initial STRUCTURE record. The requirement that the record appears is related to the possiblility just mentioned that Ω can be block diagonal, and in this case the information contained in the record is not redundant.

D.5.3. BLOCK SET Record for Ω

A DIAGONAL record for Ω does not appear in Fig. 39. Instead, a BLOCK SET record for Ω appears. The initial estimates of the elements of Ω are given in the BLOCK SET records for Ω when Ω is not constrained to be diagonal. More than one such record is only necesssary when Ω is constrained to be block diagonal, and it is this situation that gives rise to the terminology 'BLOCK SET' (see NONMEM Users Guide, Part II). Fixed point format is used. The initial estimates are placed in the fields in the following order: Ω_{11}, Ω_{12}, ..., Ω_{1K}, Ω_{22}, Ω_{23}, ..., Ω_{2K}, ..., Ω_{KK}, where K is the dimension of Ω. These estimates number K(K+1)/2 altogether. (Recall that Ω is symmetric.) If Ω is to be fixed to these initial estimates, then in addition, a 1 is placed in position 8 of the record. In the BLOCK SET record of Fig. 39, a 2 appears in position 8, and the fields are left blank, indicating that NONMEM is to obtain the initial estimates. When one field is left blank, all fields must be left blank.

D.5.4. Sorting in Tables

As mentioned in section C.3.5.3, rows of tables may be sorted on the data items in specified columns. There is some reason for utilizing this feature in the example, namely, to separate the rows with plasma concentration DV data items from those with saliva concentration DV data items. This separation may be done by selecting the P/S data items for tabulation and by indicating that the rows of the table are to be sorted firstly on these data items. Then the first rows will contain only P/S data items equal to 0, and the last rows will contain only P/S data items equal to 1. The sorting is indicated by a 1 placed in the sort field following the field containing the index of the P/S data items. Accordingly, in the individual TABLE record in Fig. 39, field 4 contains the index of the P/S data items, and a 1 is placed in the following field. There are 2 types of data items selected for tabulation (note the 2 in field 1), the P/S data items and the time data items. Since it is also useful to sort the rows with plasma concentration DV data items on their time data items, and to sort the rows with saliva concentration DV data items on their time data items, an indication that the rows are to be sorted secondly on the time data items is also given. This second level sorting (a sort within a sort) is indicated by a 2 placed in the sort field adjacent to the field following the field containing the index of the time data items. Refering to the same individual TABLE record once again, it may be seen that field 2 contains the index of the time data items, and a 2 is placed in the following field. The resulting table is given in Fig. 40.

In general, the rows of any individual table may be sorted first on the data items appearing in a specified column by placing a 1 in the sort field following the field containing the index of these data items. The rows of the table may be sorted second on the data items appearing in another specified column by placing a 2 in the sort field following the field containing the index of these data items. A third level sort may be defined similarly, and so on, up to an 8-level sort. There can be no sort on the NONMEM generated data items. These data items are not ones the user selects for tabulation, and only data items of selected types may be sorted. Although the DV data items always appear in a table, the user may explicitly select these for tabulation and thereby also sort on them. If this is done, the DV data items will appear in two columns. They will appear in the fourth column from the right as usual, and they will also appear in some other column.

The column order of the data item types selected to appear in the table corresponds to their sort codes. The data item type with sort code 1 corresponds to column 1, the data item type with sort code 2 corresponds to column 2, etc. For example, in the table of Fig. 40, the P/S data items appear in column 1, and the time data items appear in column 2. Any data item types with sort code blank or 0 correspond to columns occuring after those columns with sorted data items, and the column order of these data item types corresponds to the order in which their indices are placed in the TABLE record.

As explained in section C.3.5.3, when there are more than 900 data records, each individual TABLE record generates a number of tables, so that all data records are used. All sorting is done within each of these tables separately. This implies that if, for example, (i) sorting is specified only on ID data items, (ii) these data items are all positive integers, and (iii) the data records with ID data item equal to 1 are data records 900 and 901, then the first of these two records is used to obtain the first row in the first table, and the second record is used to obtain the first row in the second table.

D.5.5. Separating Scatterplots

A family of scatterplots may be defined by separating a given scatterplot, called the base plot, into a number of separate ones. To do this, a third data item type, called the separator, is specified, in addition to the two types of data items defining the given scatterplot. Suppose the values for the separator that appear in the data set are: v_1, v_2, ..., sorted from lowest to highest value. Then one scatterplot of the family consists of those points of the base plot resulting from all data records with the value v_1 of the separator; another consists of those points of the base plot resulting from all data records with value v_2 of the separator; etc. The family members appear in the printout in the same order as the sorted values of the separator. The family is called a one-way partitioned scatterplot.

This feature is useful in the example where it is desirable, for example, to separately plot the plasma concentrations vs their predictions, and the saliva concentrations versus their predictions. By choosing the P/S data item type for the separator, the base plot of the DV data items vs the prediction data items can be separated into the two desired plots. The P/S data item type has two values, 0 and 1. The points of the base plot resulting from all data records with P/S data item equal to 0 form one of the desired plots, while the remaining points of the base plot, resulting from all data records with P/S data item equal to 1, form the other plot.

To use this feature two additional fields of the individual SCATTERPLOT record defining the family are used. As usual, the indices of the data items defining the base plot are placed in fields 1 and 2. A 1 is placed in field 3; this indicates that one separator is used. Also, the index of the separator is placed in field 4. See, for example, the last SCATTERPLOT record of Fig. 39.

Altogether, eight families of scatterplots are defined in the problem specification of Fig. 39. Four single-member families, CONC vs TIME, PRED vs TIME, RES vs TIME, and PRED vs CONC, using the labels that appear on the scatterplots, are defined. Four two-member families are also defined, using the same base plots and using the P/S data item type as a separator. The entire set of thirteen scatterplots is given in Figs. 41-52.

Some general remarks concerning scatterplots involving residual and weighted residual data items are in order. These scatterplots are often used to detect model weaknesses. Residuals, in particular, can be scatterplotted against the values of an independent variable (a fixed effect). Ideally, the plot should have the appearance of a homogeneous scatter about the zero line. If it does not, this can suggest that the effect of the variable is not appropriately modeled, and the pattern of the scatter may suggest a more appropriate model. If there is another independent variable which can affect the data, then it can be helpful to develop a picture wherein the effects of the two variables are not confounded. Using the second variable as a separator can help in this regard. This presumes that the second variable is also a fixed effect, and that its values exist as data items in the data set. A random effect is a type of independent variable, and it also can be somewhat confounded with the effect of the first variable. The values of the random effect, however, are not known. When, though, there are several observations from some individuals, then the ID data item can be used as a separator to help distinguish random interindividual effects from the effect of the first variable.

Also, the desire for homogeneous residuals is predicated on the assumption that under the assumed model, and ignoring estimation error, the residuals are uncorrelated and have means 0 and constant variance (i.e. homogeneous variance). In each of the two examples used in this chapter, however, under the model, the variances of the observations (and therefore, of the residuals) vary with values of fixed effect independent variables. Weighted residuals, on the other hand, are uncorrelated and have means 0 and constant variance under the assumed model (and ignoring estimation error). So it is generally advisable that with models under which residuals are nonhomogeneous, weighted residuals, rather than residuals, should be plotted.

In the first example, weighted residual vs time was plotted, but in fact, the plot does not appear too different from a plot of residual vs time (not shown; but see the plot of residual vs time in Fig. 18). In the second example (the one under discussion) there really is not a need to plot weighted residuals because *when* the P/S data item type is used as a separator, the modeled variances of the observations are constant with time.

A base plot can be separated into a family based on the values of two separators. Such a family is called a two-way partitioned scatterplot. Consider all distinct pairs of values, one value from the first separator and the other value from the second separator. Then one scatterplot of the family consists of those points of the base plot resulting from the data records with one particular pair of values of the separators, and another scatterplot of the family consists of those points of the base plot resulting from the data records with another pair of values of the separators, etc. To obtain a two-way partitioned scatterplot, place a 2 in field 3 of the individual SCATTERPLOT record, and place the indices of the two separators

in fields 4 and 5.

D.5.6 Selected Printout

The summary of the problem specification shown in Fig. 39 is given in Fig. 53. Some remarks concerning it may be helpful.

The total number of individuals is stated to be 17. Due to the presence of ID data items, individual records are defined, and the number of such records may be verified to be 17.

The matrix Ω is stated to have a certain block form. Its lower triangular part is shown schematically to indicate that it is a simple 2×2 matrix. The matrix could be constrained to have a block diagonal form, in which case this form would be indicated with a more "interesting" schematic pattern than that shown in this problem summary (see NONMEM Users Guide, Part II).

The final parameter estimate, standard errors, and correlation matrix are shown in Figs. 54-56. The reader might note that the correlation between η_{1i} and η_{2i} is estimated to be -0.066, which is quite small.

E. Linear Regression with One-Level Nested Random Effects

E.1. Introduction

In this chapter two examples, using some new type of data, are considered. The data are typical of repeated measures type data and can be modeled using one-level nested random effects. Also, the data can be modeled using a linear, rather than a nonlinear, regression function. This simplification allows the reader to better focus on the considerations involving the random effects. However, use of a linear regression function is also very common with repeated measures type data. (An example involving a nonlinear regression function is given in chapter F.) One example involves one random interindividual effect and one random intraindividual effect. It is discussed in sections E.2 and E.3. Another example, a multivariate regression and with two random effects of each type, is discussed in sections E.4 and E.5.

E.2 Example with One Inter- and One Intra-Individual Random Effect

In this example six oral doses of theophylline were administered to each of a number of subjects. With each subject the doses were given at times when no drug from previous doses remained in the subject. For each dose, a measurement called the (observed) drug clearance for the subject, was made using the measured drug concentration vs time data resulting from the dose after absorption was complete. Drug clearance has the form: dose divided by area under the concentration vs time curve. It is a measurement of the elimination chracteristics of the drug (The clearance might be given by the formula $\bar{\theta}_2\bar{\theta}_3$, where $\bar{\theta}_2$ and $\bar{\theta}_3$ are estimates of the rate constant of elimination and volume of distribution, obtained from the concentration vs time data as in previous examples. However, in this example the clearance was computed nonparametrically.) The observations are these clearances. The subject's weight is often an important explanatory variable of his clearance, and weight data items are included in the data set. The pharmacokinetic model for theophylline plasma concentration is linear in dose (see the previous examples), and therefore clearance is assumed to be independent of dose.

The statistical model for the jth observation from the ith individual is taken to be

$$y_{ij} = \theta_1 x_{ij} + \theta_2 + \eta_i + \varepsilon_{ij}$$

where θ_1 and θ_2 are regression parameters, x_{ij} denotes weight, the η_i are statistically independent values of random interindividual effects, with means 0 and common variance Ω (a scalar), and the ε_{ij} are statistically independent values of random intraindividual effects, with means 0 and common variance Σ (a scalar). A value of the random interindividual effect, η_i, is always taken to be statistically independent of a value of the random intraindividual effect, ε_{ij}. The variable x is doubly subscripted, suggesting that for each individual, its value can vary between doses. In fact, though, in the actual data set its value remains constant across doses for each individual. The regression function is linear in weight. Since if this linearity holds, it may do so only over a limited weight range, an intercept parameter might be included in the model. However, analysis of the data has revealed no evidence whatsoever of a nonzero intercept. Consequently, while an intercept parameter has in fact been included in the model, in this example it shall be constrained to be 0. Under the model, the observations y_{i1}, y_{i2}, ..., y_{i6} are each affected by η_i, and so they are correlated. We let y_i denote the column form of the vector consisting of the six observations, $(y_{i1}, y_{i2}, \ldots, y_{i6})$. The random intraindividual effect is clearly nested within the random interindividual effect. For each value of the random interindividual effect, the random intraindividual effect takes on six different values, while for no value of the random intraindividual effect does the random interindividual effect take on different values. (These effects are presumed to be continuously distributed.)

The NONMEM linear model schematic is given by

$$y_{ij} = f_{ij}(\theta) + g_{ij}\eta_i + h_{ij}\varepsilon_{ij}$$

where

$$f_{ij}(\theta) = \theta_1 x_{ij} + \theta_2$$

$$g_{ij} = 1$$

$$h_{ij} = 1$$

Let I denote the number of individuals. Also, for fixed i, let f_i denote the column vector of values of the f_{ij}, let g_i denote the column vector of values of the g_{ij} (viz. a column vector of 1's), and let h_i denote the column vector of values of the h_{ij} (viz. a column vector of 1's). Then the ELS objective function is given by

$$O(\theta, \Omega, \Sigma) = \sum_{i=1}^{I} \left[\log \det C_i(\Omega, \Sigma) + R_i(\theta, \Omega, \Sigma)' R_i(\theta, \Omega, \Sigma) \right]$$

where

$$R_i(\theta, \Omega, \Sigma) = C_i(\Omega, \Sigma)^{-1/2}(y_i - f_i(\theta))$$

$$C_i(\Omega, \Sigma) = g_i \Omega g_i' + \text{diag}\,(h_i \Sigma h_i')$$

and where if A is a square matrix, diag (A) denotes the diagonal matrix whose diagonal elements are those of A. The matrix C_i is the variance-covariance matrix of y_i. The vector R_i is the vector of weighted residuals from the observations y_i. As with previous examples, it has the form residual (vector) divided by standard deviation (matrix), and it is "squared" in the expression for the objective function. The weighted residuals are defined to be the weighted residuals from all obervations y_i. It may be seen that the form of the objective function is the same as that given with previous examples, except that now C_i has an extra term expressing intraindividual variability which for the first time is a factor.

E.3. Implementation of Example 1 E.3.1. Inputs

A code for PRED which implements the example is given in Fig. 57. Note that the values g_{ij} and h_{ij} are returned in G(1) and H(1), respectively. These are the coefficients of η_i and ε_{ij} in the NONMEM linear model schematic. In general, the value returned in G(I) is the coefficient of the Ith random interindividual effect in the NONMEM linear model schematic, and the value returned returned in H(I) is the coefficient of the Ith random intraindividual effect in the NONMEM linear model schematic.

A control stream for this example is given in Fig. 58. The data set is embedded in it, and the data items in a data record are the ID, weight, and DV data items, respectively.

Since in the example there are both random inter- and intra-individual effects, there are entries in both fields 2 and 3 of the initial STRUCTURE record. In general, the numbers of random interindividual effects and random intraindividual effects are placed in fields 2 and 3, respectively. The total number of both random inter- and intra-individual effects cannot exceed 10. Also, since in the example both Ω and Σ are taken to be diagonal (they are both scalars), there are 1's in both fields 6 and 8. In general, if Ω is constrained to be diagonal, a 1 is placed in field 6, and if Σ is constrained to be diagonal, a 1 is placed in field 8. If Ω (Σ) is not constrained, a 1 is placed in field 7 (9). (Since a scalar is also an unconstrained 1×1 matrix, in this example a 1 could be placed in either field 7 or 9, but a more perspicuous problem summary develops when a scalar is regarded as a diagonal matrix.)

The initial estimate of θ_1 is obtained by first averaging all the 72 clearances to obtain an estimate of mean clearance in the population. (This is equivalent to averaging the 6 clearances in each of the 12 individuals to obtain to obtain estimates of the individuals' mean clearances, and then averaging these 12 individual estimates.) Then this estimate is divided by 70Kg, the average weight of the individuals of the

sample, to obtain the desired estimate. Since lower and upper bounds of 0 are specified for θ_2 (thus this parameter is fixed to 0), lower and upper bounds must also be specified for θ_1, but these are taken to be $-\infty$ and ∞ (see sections C.3.4.4 and C.3.4.5).

Since in the example the two parameters Ω and Σ must be estimated, as well as θ, there must be initial estimates specified for each. Therefore, a DIAGONAL record for Σ, as well as a DIAGONAL record for Ω appears in the problem specification. Its form is exactly that of the DIAGONAL record for Ω. The initial estimate record for Σ (be it a DIAGONAL or BLOCK SET record) is placed after the initial estimate record for Ω (be it a DIAGONAL or BLOCK SET record).

Unlike previous examples, for illustrative purposes, actual initial estimates have been placed in both DIAGONAL records, rather than letting the fields be blank. The initial estimate of Σ is obtained by first obtaining for each individual, the sample variance of his clearance measurements. Then these individual estimates are averaged to obtain the desired estimate. The initial estimate of Ω is obtained by first calculating the sample variance of the individuals' average clearances. Then 1/6 of the the initial estimate of Σ is subtracted from this sample variance to obtain the desired estimate. In this example the same final estimate, standard errors, etc. are obtained when the fields of the DIAGONAL records are left blank.

E.3.2 Selected Printout

The final parameter estimate, standard errors, and correlation matrix are shown in Figs. 59-61. Note that in these printouts θ_2 is listed. Its final estimate is 0, the value to which the parameter is fixed. The covariance (or correlation) of any estimate of a fixed parameter with the estimate of any other parameter is by definition 0. However, lest the user forget this and think that a number other than 0 could appear for the estimate of this covariance (or correlation), but that 0 is in fact the estimate, a 0 does not in fact appear in the printout. Instead, a place holder consisting of dots appears in order to remind the user that the covariance (correlation) is 0 by definition. Similarly, this type of place holder also appears for the standard error estimate of the point estimate of a fixed parameter.

The two scatterplots of residual vs weight and weighted residual vs weight are shown in Figs. 62 and 63. It is not necessary to separate these scatterplots by ID since in this example weight is in effect a surrogate for ID, and so the residuals are already very naturally separated by individual. However, to better look for homogeneous scatter, it is better to examine the scatterplot of weighted residual vs weight. In this example the weighted residuals are distributed much more homogeneously about the zero line than are the residuals.

E.4. Example with Two Inter- and Two Intra-individual Random Effects

This is an extension of example 1. Again, six oral doses are given to each of 12 subjects, and with each dose a clearance is measured. In addition, with each dose a rate constant of elimination is measured. This measurement is an estimate of the parameter θ_2 in the example of section D.4, obtained graphically from the plasma concentration vs time data ocurring after the absorption phase is over. The clearance and rate constant may correlate across doses within any individual. Therefore, the clearance and rate constant together form a bivariate observation from the point of view of random intraindividual variablity. There are altogether 6 such bivariate observations per individual.

The statistical model for the kth element of the jth (bivariate) observation from the ith individual is taken to be

$$y_{ijk} = \theta_1 x_{1ijk} + \theta_2 + \eta_{1i} + \varepsilon_{1ijk}$$

$$\text{if } x_{2ijk} = 0$$

$$y_{ijk} = \theta_3 + \eta_{2i} + \varepsilon_{2ijk}$$

$$\text{if } x_{2ijk} = 1$$

where x_2 is a clearance-rate constant indicator variable (0: clearance; 1: rate constant). Here the new part of the model is the part for the rate constant measurement. The mean rate constant measurement is simply assumed to be a constant and not to vary with weight. The error structure for the rate constant measurements is analogous to that for the clearance mesurements; it is the sum of both simple interindividual and simple intraindividual error. The variance-covariance matrix of $\eta_i = (\eta_{1i}, \eta_{2i})$ is the 2×2 matrix Ω, and the variance-covariance matrix of $\varepsilon_{ij} = (\varepsilon_{1ij}, \varepsilon_{2ij})$ is the 2×2 matrix Σ. A value of the random interindividual effect vector η_i is always statistically independent of a value of the random intraindividual effect vector ε_{ij}. Under the model the clearance observations from individual i are each affected by the η_{1i}, the rate constant observations from individual i are each affected by η_{2i}, and η_{1i} and η_{2i} are correlated, and so all the observations from individual i are correlated. Each pair of clearance and rate constant observations with a given dose are also correlated by virtue of the correlation between the two random intraindividual effects. We let y_i denote the column form of the vector consisting of the twelve observations, $(y_{i11}, y_{i12}, y_{i21}, y_{i22}, \ldots, y_{i61}, y_{i62})$. The random intraindividual effects are clearly nested within the random interindividual effects.

The NONMEM linear model schematic is given by

$$y_{ijk} = f_{ijk}(\theta) + g_{1ijk}\eta_{1i} + g_{2ijk}\eta_{2i} + h_{1ijk}\varepsilon_{1ij} + h_{2ijk}\varepsilon_{2ij}$$

where

$$f_{ijk}(\theta) = \theta_1 x_{ijk} + \theta_2$$

$$\text{if } x_{2ijk} = 0$$

$$f_{ijk}(\theta) = \theta_3$$

$$\text{if } x_{2ijk} = 1$$

$$g_{1ijk} = 1 \text{ or } 0$$

$$\text{if } x_{2ijk} = 0 \text{ or } 1, \text{ respectively}$$

$$g_{2ijk} = 0 \text{ or } 1$$

$$\text{if } x_{2ijk} = 0 \text{ or } 1, \text{ respectively}$$

$$h_{1ijk} = 1 \text{ or } 0$$

$$\text{if } x_{2ijk} = 0 \text{ or } 1, \text{ respectively}$$

$$h_{2ijk} = 0 \text{ or } 1$$

$$\text{if } x_{2ijk} = 0 \text{ or } 1, \text{ respectively}$$

Let I denote the number of individuals. Also, for fixed i, let f_i denote the column vector of values of the f_{ijk}, let g_{1i} denote the column vector of values of the g_{1ijk}, let g_{2i} denote the column vector of values of the g_{2ijk}, let h_{1i} denote the column vector of values of the h_{1ijk}, and let h_{2i} denote the column vector of values of the h_{2ijk}. Then the ELS objective function is given by

$$O(\theta, \Omega, \Sigma) = \sum_{i=1}^{I} \left[\log \det C_i(\Omega, \Sigma) + R_i(\theta, \Omega, \Sigma)' R_i(\theta, \Omega, \Sigma) \right]$$

where

$$R_i(\theta, \Omega, \Sigma) = C_i(\Omega, \Sigma)^{-1/2}(y_i - f_i(\theta))$$

$$C_i(\Omega, \Sigma) = (g_{1i}, g_{2i})\Omega(g_{1i}, g_{2i})' + \text{diag}_2((h_{1i}, h_{2i})\Sigma(h_{1i}, h_{2i})')$$

and where if A is a square matrix, diag_2 (A) denotes the block diagonal matrix whose diagonal blocks are the 2×2 diagonal blocks of A. The matrix C_i is the variance-covariance matrix of y_i. The vector R_i is the vector of weighted residuals from the observations y_i. As with previous examples, it has the form residual (vector) divided by standard deviation (matrix), and it is "squared" in the expression for the objective function. The weighted residuals are defined to be the weighted residuals from all obervations y_i.

E.5 Implementation of Example 2

E.5.1 Inputs

A code for PRED which implements the example is given in Fig. 64. The computation involves querying the value of x_2. Note that the values g_{1ij} and g_{2ij} are returned in G(1) and G(2), respectively. These are the coefficients of η_{1i} and η_{2i} in the NONMEM linear model schematic. In general, the value returned in G(I) is the coefficient of the Ith random interindividual effect in the NONMEM linear model schematic. The values h_{1ij} and h_{2ij} are returned in H(1) and H(2), respectively. These are the coefficients of ε_{1ij} and ε_{2ij} in the NONMEM linear model schematic. In general, the value returned in H(I) is the coefficient of the Ith random intraindividual effect in the NONMEM linear model schematic.

A control stream for this example is given in Fig. 65. The data set is embedded in it, and the data items in a data record are the ID data item, the weight data item, the DV data item, the clearance-rate constant indicator data item (x_2), and the level-two data item, respectively. This last type of data item is needed with one-level nested random effects in order to group together the DV data items belonging to a bivariate observation (see section B.1). It is given the label L2 in the NONMEM printout, and the ID data item is given the label L1 since in this example the ID data item is also the level-one data item. Note that for readability and for the purpose of conveniently keying the data, the indicator data item is blank in those places where it is actually zero, and similarly with the level-two data item. The alternating use of the values 0 and 1 for the level-two data items illustrates how it is not necessary that noncontiguous level-two records have different level-two data items. Note that the index of the level-two data item is placed in field 7 of the ITEM record.

The initial STRUCTURE record for the problem specification has 1's in fields 7 and 9, indicating that both Ω and Σ are full matrices, i.e. neither is constrained to be diagonal. When a 1 is placed in field 7 (9) of the initial STRUCTURE record, the number of random inter- (intra-) individual effects cannot exceed 5.

The control stream contains a STRUCTURE record for Σ, as well as a STRUCTURE record for Ω. This is, of course, because neither Ω nor Σ is constrained to be a diagonal matrix. The form of the STRUCTURE record for Σ is exactly that of the STRUCTURE record for Ω (see section D.5.2). When the STRUCTURE record for Σ appears, it is placed after the STRUCTURE record for Ω, except when the latter record is not present, in which case the STRUCTURE record for Σ is placed after the initial

STRUCTURE record.

The initial estimate for θ_1 is that used in the previous example. The initial estimate of θ_3 is obtained by averaging the 72 rate constant measurements.

The control stream contains a BLOCK SET record for Σ, as well as a BLOCK SET record for Ω. The form of the BLOCK SET record for Ω is exactly that of the BLOCK SET record for Ω (see section D.5.3).

The initial estimate of Σ is obtained by first obtaining for each individual, the sample variance-covariance matrix of his clearance and rate constant measurements. Then these individual matrix estimates are averaged to obtain the desired estimate. The initial estimate of Ω is obtained by first calculating the sample variance-covariance matrix of the individuals' average clearances and average rate constants. Then 1/6 of the the initial estimate of Σ is subtracted from this sample variance-covariance matrix to obtain the desired estimate. In this example the same final estimate, standard errors, etc. are obtained when the fields of the BLOCK SET records are left blank.

E.5.2 Selected Printout

The final estimate, standard errors, and correlation matrix are shown in Figs. 66-68. It is interesting to compare the final estimates and standard errors from this example with those from the previous example. All the parameters associated with clearance only that occur in the model with the previous example also occur in the extension of that model which is considered here, and in this extended model the only parameter associated with both clearance and rate constant is the covariance parameter in Ω. Consequently, the final estimates and standard errors of the estimates from this example are very close to those from the previous example.

Regarding the covariance parameter Ω_{12}, note that its normalized value, i.e. the correlation between η_1 and η_2 ($\Omega_{12}/(\Omega_{11}\Omega_{22})^{1/2}$), is estimated to be .95. (Whereas the minimum value of the objective function is -651, in another NONMEM run where Ω is constrained to be DIAGONAL the minimum value is much larger -631, indicating that the correlation is indeed significant.) This suggests that variablity in estimates of volume of distribution that might be obtained across individuals and doses would be due largely to random intraindividual (dose to dose) variablity and little to random interindividual variablity. The reason for this is as follows. As noted in section E.2, a clearance observation for a given individual and dose might have been measured by $\bar{\theta}_2\bar{\theta}_3$, where $\bar{\theta}_2$ and $\bar{\theta}_3$ are estimates of the rate constant of elimination and volume of distribution obtained from concentration vs time data. As noted in section E.4, a rate constant observation for a given individual and dose might have been measured by $\bar{\theta}_2$. The high interindividual correlation between these two types of measurements implies an approximately proportional interindividual relationship between $\bar{\theta}_2\bar{\theta}_3$ and $\bar{\theta}_2$, i.e. an approximately constant interindividual relationship for θ_3.

The first and last pages of the requested table are shown in Fig. 69. The scatterplots of residual vs weight separated by TYPE are given Figs. 70 and 71. The scatterplots of weighted residual vs weight separated by TYPE are given in Figs. 72 and 73.

F. Nonlinear Regression with One-Level Nested Random Effects

F.1 An Example

In this chapter we return to theophylline plasma concentration vs time data, but where such data from 12 subjects, rather than from a single subject, are available. This is done to illustrate a regression with one-level nested random effects where the regression function is nonlinear. The fact that the regression function is nonlinear really does not introduce any new considerations regarding the inputs required by NONMEM. However, often with a nonlinear regression function and one-level nested random effects, a modeling approximation is necessary, and this is described here. Also, this example does bring together a number of concepts discussed in the earlier examples.

Each subject is given a single oral dose, the same dose for each subject. Each subject has a different weight. Often dose is expressed as the amount of drug administered per unit weight of the subject (weight-adjusted dose), and in this example the dose data item is the weight-adjusted dose. However, a weight data item is also included in the data record because it will be assumed that interindividual differences in plasma concentrations may be due to interindividual weight differences beyond those expressed through weight-adjusted dose. Also, 11 plasma concentrations are observed per individual at different times, and these times vary between individuals. (The clearance and rate constant measurements used in the examples of chapter E are obtained from this concentration vs time data and from similar data using an additional five doses per subject.)

A model for the jth observation from the ith individual might be given by

$$y_{ij} = F(\theta_1, \theta_2, \theta_3, \eta_{1i}, \eta_{2i}, \eta_{3i}, x_{1i}, x_{2ij}, x_{3i}) = \frac{\kappa_{1i}\kappa_{2i}x_{1i}}{\kappa_{3i}(\kappa_{1i} - \kappa_{2i})} (\exp(-\kappa_{2i}x_{2ij}) - (\exp(-\kappa_{1i}x_{2ij})) + \varepsilon_{ij}$$

where

$$\kappa_{1i} = \theta_1 + \eta_{1i}$$

$$\kappa_{2i} = \theta_2 + \eta_{2i}$$

$$\kappa_{3i} = \theta_3 x_{3i} + \eta_{3i}$$

where x_1, x_2, and x_3 are the (non-weight-adjusted) dose, time, and weight variables. Here x_1 and x_3 are not subscripted with a j, indicating that the values of the dose and weight variables do not vary within the individual. This model is similar to one used in chapter C for data from a single individual, but there are some notable differences. First, the ith individual is regarded as having his own set of pharmacokinetic parameters, these parameters are denoted by κ_{1i}, κ_{2i}, and κ_{3i}. Second, two of the pharmacokinetic parameters are rate constant of absorption, κ_{1i}, and rate constant of elimination, κ_{2i}, as previously, but the third basic parameter is clearance, κ_{3i}, rather than volume of distribution. Third, these parameters are affected by random interindividual affects, and thus random interindividual variability is expressed in the model. Fourth, residual error is an intraindividual effect. Note that an individual's clearance is linearly related to his weight as in chapter E. The variance-covariance of the random interindividual effects, Ω, is regarded as a full matrix in this example.

As stated in section A.1, with the current version of NONMEM random effects must enter the model (for the observations) linearly. This requirement is not met in the above model; the random interindividual effects enter nonlinearly. One device that has been found useful under these circumstances is to approximate the above model, A, with another, B, obtained by expanding A with a first-term Taylor Series in the random effects about their mean values (0). In the case at hand B is given by

$$y_{ij} = f_{ij}(\theta_1, \theta_2, \theta_3) + g_{1ij}(\theta_1, \theta_2, \theta_3)\eta_{1i} + g_{2ij}(\theta_1, \theta_2, \theta_3)\eta_{2i} + g_{3ij}(\theta_1, \theta_2, \theta_3)\eta_{3i} + h_{ij}\varepsilon_{ij}$$

where

$$f_{ij}(\theta_1, \theta_2, \theta_3) = F(\theta_1, \theta_2, \theta_3, 0, 0, 0, x_{1i}, x_{2ij}, x_{3i})$$

$$g_{1ij}(\theta_1, \theta_2, \theta_3) = \frac{\partial F}{\partial \eta_{1i}}(\theta_1, \theta_2, \theta_3, 0, 0, 0, x_{1i}, x_{2ij}, x_{3i})$$

$$g_{2ij}(\theta_1, \theta_2, \theta_3) = \frac{\partial F}{\partial \eta_{2i}}(\theta_1, \theta_2, \theta_3, 0, 0, 0, x_{1i}, x_{2ij}, x_{3i})$$

$$g_{3ij}(\theta_1, \theta_2, \theta_3) = \frac{\partial F}{\partial \eta_{3i}}(\theta_1, \theta_2, \theta_3, 0, 0, 0, x_{1i}, x_{2ij}, x_{3i})$$

$$h_{ij} = 1$$

Written this way, the model is also displayed as the NONMEM linear model schematic. Use of this first-order approximation to the original model, along with use of the ELS objective function, has been called the First-Order Method for analyzing nonlinear mixed effects modeled data. This method has been shown to be statistically efficacious in particular situations (Sheiner and Beal, 1980, 1981, and 1983, and Beal 1984a). The first-order approximation itself may be called the First-Order Model. One practical problem with this method is that it can require some nontrivial effort to obtain the partial derivatives defining the g's. Moreover, there is little to be gained by examining these derivatives. Indeed, rather than try to display explicit formulae for the g's in this example in this text, we refer the reader to the PRED routine of Fig. 73 where code is given for these formulae. Certain tools are available to help the user obtain the first-order model. PREDPP is a package which can be used with NONMEM and with pharmacokinetic data and which automatically obtains the derivatives $\partial F/\partial \kappa_{mi}$, when, as in the example, the effect of the η's is through κ's. PREDPP is actually a very elaborate PRED subroutine. It then remains for the user to supply code for the derivatives $\partial \kappa_{mi}/\partial \eta_{ni}$; these are relatively simple to obtain. Also, NM-TRAN, a computer program which facilitates the problem of constructing inputs to NONMEM, can be used to automatically obtain the derivatives $\partial \kappa_{mi}/\partial \eta_{ni}$. (Both PREDPP and NM-TRAN are distributed with NONMEM.)

Let I denote the number of individuals. Also, for fixed i, let f_i denote the column vector of values of the f_{ij}, let g_{1i} denote the column vector of values of the g_{1ij}, let g_{2i} denote the column vector of values of the g_{2ij}, let g_{3i} denote the column vector of values of the g_{3ij}, and let h_i denote the column vector of values of the h_{ij}. Then the ELS objective function is given by

$$O(\theta, \Omega, \Sigma) = \sum_{i=1}^{I} \left[\log \det C_i(\theta, \Omega, \Sigma) + R_i(\theta, \Omega, \Sigma)' R_i(\theta, \Omega, \Sigma) \right]$$

where

$$R_i(\theta, \Omega, \Sigma) = C_i(\theta, \Omega, \Sigma)^{-1/2}(y_i - f_i(\theta))$$

$$C_i(\theta, \Omega, \Sigma) = (g_{1i}(\theta), g_{2i}(\theta), g_{3i}(\theta)\Omega(g_{1i}(\theta), g_{2i}(\theta), g_{3i}(\theta)' + \text{diag}(h_i \Sigma h_i')$$

The last term in the expression for C_i is just a fancy way of writing the diagonal matrix whose elements are all Σ. The matrix C_i is the variance-covariance matrix of y_i. The vector R_i is the vector of weighted residuals from the observations y_i. As with previous examples, it has the form residual (vector) divided by standard deviation (matrix), and it is "squared" in the expression for the objective function. The weighted residuals are defined to be the weighted residuals from all obervations y_i.

F.2 Implementation of the Example

F.2.1 Inputs

A code for PRED which implements the example is given in Fig. 74. It is similar to that in Fig. 1. However, the values returned in G are now very different, and a value is also returned in H. The same rules for determining what is returned in G and H, and that are given in chapter E, apply here too. For clarity, code to compute the partial derivatives that are returned in G is indented from the other code. Note that in the expression for F the weight-adjusted dose (DOSE) appears, rather than the non-weight-adjusted dose, but that also THETA(3) occurs in the denominator (E=THETA(3)*C) of that same expression, so that weight itself need not enter this expression. On the other hand, since $\eta_{3\,i}$ adds to mean clearance, weight does enter the expression for G(3).

A control stream for this example is given in Fig. 75. The data set is embedded in it. Note that for readability and for the purpose of conveniently keying the data, the weight-adjusted dose and weight data items are blank for all data records of an individual record except the first data record. The PRED routine stores these data items in its local storage whenever the first data record of an individual record is passed to it (review the argument NEWIND described in section C.3.5.2).

The initial STRUCTURE record for the problem specification has 1's in fields 7 and 8, indicating that Ω is a full matrix, but that Σ is constrained to be diagonal. (Again, since Σ is a scalar, it can be regarded as an unconstrained 1×1 matrix, but for the sake of a more perspicuous problem summary, it is taken to be diagonal.)

F.2.2 Selected Printout

The final estimate, standard errors, and correlation matrix are shown in Figs. 76-78. It may interest the reader to see how remarkably well the final estimates in Figs. 66 and 76 agree for those parameters that occur in both the model in section E.4 and the model in section F.1. The final estimates of these parameters from both figures, their standard errors, and the ratios of standard error to estimate are given in Table F.2.2.i. Recall that the estimates in Fig. 76 are obtained using one-sixth the amount of data used to obtain the estimates in Fig. 66, since in the present example only the concentration data from one dose per individual are used, while in the previous example this same data, plus similar data from five additional doses per individual, are used.

Table F.2.2.i
Estimate Comparison

Parameter	Sec.	Est.	S.E.	S.E./Est. (%)
slope	E.4	.0446	.00230	5.2
	F.1	.0363	.00466	12.9
mean rate const.	E.4	.0843	.003698	4.4
	F.1	.0781	.00736	9.4
Ω_{22}	E.4	.327	.162	49.5
	F.1	.515	.208	40.4
Ω_{33}	E.4	.000154	.0000905	58.3
	F.1	.000240	.000118	46.7
Ω_{23}	E.4	.00672	.00371	55.2
	F.1	.00911	.00362	39.7

The first page of the requested table is shown in Fig. 79. Scatterplots of residual vs time and of weighted residual vs time, both separated by ID, are requested. The four scatterplots corresponding to individuals 4 and 5 are shown as examples in Figs. 80-83.

G. Error Messages

G.1 Messages from Processing Data Records

The data records are checked for three possible errors. Each error generates a message given below.

A) MDV DATA ITEM FOR DATA REC NO. n IS INAPPROPRIATE

Explanation: The MDV data item in data record no. n is neither 0 nor 1.

System Action: Program terminates when encountering first such record.

B) TOT. NO. OF OBSERVATIONS IN INDIVIDUAL REC NO. n
(IN INDIVIDUAL REC ORDERING) EXCEEDS 50

Explanation: The maximum number of observation records allowed in any individual record is 50. Individual record no. n does not comply with this limitation.

System Action: Program terminates when encountering first such record.

User Response: If there are important reasons for using more than 50 observation records in an individual record, the limit of 50 may be increased; see NONMEM Users Guide, Part III. This will entail recompiling parts of NONMEM. Execution time increases rapidly with the number of observation records per individual record.

C) WARNING: NO. OF OBS RECS IN INDIVIDUAL REC NO. n
(IN INDIVIDUAL REC ORDERING) EXCEEDS ONE
WHILE INITIAL ESTIMATE OF WITHIN INDIVIDUAL VARIANCE IS ZERO

Explanation: The initial estimate of Σ is fixed to 0, while intraindividual variability appears to exist in the data. Moreover, the Simulation Step is not implemented.

System Action: Continue processing. Message is issued only with the first five individual records in which the number of observation records exceeds one.

User Response: If it is not intended that the number of observation records in individual record no. n should exceed one, then correct the data set. If it is not intended that the initial estimate of Σ should be 0, then check the initial estimate. There can be circumstances where the intent is to have multiple observations in individual records and to fix Σ to 0. In these circumstances the random intraindividual effects in the model have no actual effect on the data since Σ is 0 and so their values are constant. However, another way to arrange that random intraindividual effects have no effect is to eliminate them from the model. This is accomplished by placing a 0 in field 3 of the initial STRUCTURE record and by omitting all control records pertaining to Σ.

G.2 Messages from Processing Control Records

Each control record is checked for many possible errors, such as there being an integer in a control record outside the permitted range, or there being a sort code in a TABLE record which appears more than once in the record. If an error is found in a control record, a self-explanatory error message is printed that directs the user to examine this record, and sometimes the particular field(s) containing the error. One control record after another is checked, and when the first control record (or combination of control records) with an error is found, NONMEM issues the appropriate error message and terminates. Therefore, subsequent control records with errors may not be identified until a subsequent NONMEM run.

G.3 Messages from the Estimation Step

Besides one possible error message from the Estimation Step, there are the three lines of output that always appear and that describe the nature of the termination of the minimization search. In addition, with the default ELS objective function a certain pattern of output indicates that with the initial parameter estimate, the estimated variance-covariance matrix of some individual's set of observations is algorithmically singular. This pattern can also occur with a user-specified objective function when with the initial parameter estimate the user-supplied subprogram CONTR issues return code 1. (See NONMEM Users Guide II.) The pattern consists of a) termination of the search after the second iteration due to rounding errors dominating, b) an exceedingly large value of the objective function at the end of the 0th, 1st, and 2nd iterations, c) zero gradients (across all STP) at these three iterations, d) asterisks for the minimum value of the objective function, and e) a final estimate equalling the initial estimate. In this case user response should be to check i) that a suitable model has been chosen for the data, ii) for programming errors in PRED, iii) that reasonable initial estimates have been specified, iv) for mistakes in the data set. When the Estimation Step is not implemented, a pattern consisting of asterisks for the minimum value of the objective function should also prompt the same user response.

The error message from the Estimation Step is:

A) PROGRAM TERMINATED BY OBJ, ERROR IN CONTR
WITH INDIVIDUAL n (IN INDIVIDUAL RECORD ORDERING)
RETURN CODE m

Explanation: CONTR is the user-supplied subprogram for computing the contribution made to the objective function from a given individual's data. It has encountered an error with individual n, and it has issued a return code m > 1.

System Action: Program terminates.

User Response: Response should be appropriate for return code m.

G.4 Messages from the Covariance Step

The following error messages from the Covariance Step either indicate the reasons why various anticipated output is omitted from the Covariance Step or give a warning. The system action in each case is to continue processing. Reference is made to the R and S matrices. These matrices, computed in the Covariance Step, are described in NONMEM Users Guide, Part II. The R matrix is a numerical approximation to the hessian matrix of the objective function evaluated at the final estimate. As such, it is desireable that it be nonsingular and positive semidefinite. If it is not, then the covariance matrix may not be obtainable. If the S matrix is singular, then the inverse covariance matrix may not be obtainable.

A) R MATRIX UNOBTAINABLE

B) S MATRIX UNOBTAINABLE

C) R MATRIX ALGORITHMICALLY SINGULAR

D) R MATRIX ALGORITHMICALLY SINGULAR
AND ALGORITHMICALLY NON-POSITIVE SEMIDEFINITE

E) R MATRIX ALGORITHMICALLY NON-POSITIVE SEMIDEFINITE
BUT NONSINGULAR

F) S MATRIX ALGORITHMICALLY SINGULAR

G) PSEUDO INVERSE OF S MATRIX UNOBTAINABLE

H) PSEUDO INVERSE OF COVARIANCE MATRIX UNOBTAINABLE

I) EIGENVALUES NO. n AND GREATER UNOBTAINABLE

When messages A and B occur, they are accompanied by the messages:

J) ERROR RMATX-n m

K) ERROR SMATX-n m

respectively. These two messages are not explained here. If message C occurs, the objective function could be flat over some part of the parameter space that includes the final estimate. If message D or E occurs, the final estimate is not a local minimum. A situation giving rise to one of the above messages may also give rise to one of the following messages which indicate that certain output is being ommitted or indicates that surrogate output is generated.

L) COVARIANCE MATRIX UNOBTAINABLE

M) INVERSE COVARIANCE MATRIX UNOBTAINABLE

N) COVARIANCE MATRIX SET EQUAL TO INVERSE OF R MATRIX

O) COVARIANCE MATRIX SET EQUAL TO INVERSE OF S MATRIX

P) INVERSE OF COVARIANCE MATRIX SET EQUAL TO R MATRIX

Q) INVERSE OF COVARIANCE MATRIX SET EQUAL TO S MATRIX

If the covariance matrix is unobtainable, so are the standard errors and the correlation matrix.

In addition to messages A-Q, these two messages can occur together:

R) PROGRAM TERMINATED BY OBJ, ERROR IN ELS
VAR-COV WITH INDIVIDUAL n (IN INDIVIDUAL RECORD ORDERING)
ESTIMATED TO BE ALGORITHMICALLY SINGULAR

S) MESSAGE ISSUED FROM COVARIANCE STEP

Explanation: With the final parameter estimate, the estimated variance-covariance matrix of the observations from individual n is algorithmically singular.

System Action: Program terminates.

User Response: The error can occur only when the final estimate is the initial estimate and only when either the Covariance Step is unconditionally implemented or a MSF is used. Respond with i-iv, as indicated in section G.3. If MSF is used, check that it is the correct one.

These two messages may also occur together:

T) PROGRAM TERMINATED BY OBJ, ERROR IN CONTR
WITH INDIVIDUAL n (IN INDIVIDUAL RECORD ORDERING)
RETURN CODE m

U) MESSAGE ISSUED FROM COVARIANCE STEP

Explanation: CONTR is the user-supplied subprogram for computing the contribution made to the objective function from a given individual's data. It has encountered a fatal error with individual n, and it has issued a return code m.

System Action: Program terminates.

User Response: The error can occur only when the final estimate is the initial estimate and only when either the Covariance Step is unconditionally implemented or a MSF is used. Respond with i-iv, as indicated in section G.3. If MSF is used, check that it is the correct one. Response should be appropriate for return code m.

G.5 Messages from the Table and Scatterplot Steps

These two messages may can occur together:

A) PROGRAM TERMINATED BY PRRES, ERROR IN ELS
VAR-COV WITH INDIVIDUAL n (IN INDIVIDUAL RECORD ORDERING)
ESTIMATED TO BE ALGORITHMICALLY SINGULAR

B) MESSAGE ISSUED FROM x STEP

Explanation: With the final parameter estimate, the estimated variance-covariance matrix of the observations from individual n is algorithmically singular. In message B the x stands for either TABLE or SCATTERPLOT, whichever applies.

System Action: Program terminates.

User Response: The error can occur only when the final estimate is the initial estimate and only when the Estimation Step is either unconditionally implemented or not implemented. Respond with i-iv, as indicated in section G.3.

These two messages may also occur together:

C) PROGRAM TERMINATED BY PRRES, ERROR IN CONTR

WITH INDIVIDUAL n (IN INDIVIDUAL RECORD ORDERING)
RETURN CODE m

D) MESSAGE ISSUED FROM x STEP

Explanation: CONTR is the user-supplied subprogram for computing the contribution made to the objective function from a given individual's data. It has encountered a fatal error with individual n, and it has issued a return code m. In message D the x stands for either TABLE or SCATTERPLOT, whichever applies.

System Action: Program terminates.

User Response: The error can occur only when the final estimate is the initial estimate and only when the Estimation Step is either unconditionally implemented or not implemented. Respond with i-iv, as indicated in section G.3. Response should be appropriate for return code m.

There is another possible message from the Scatterplot Step:

E) RANGE FOR x is ZERO

Explanation: The data items labeled x are to be scatterplotted, but they are all equal.

System Action: Replace the scatterplot with this message.

G.5 Messages from the Finalization Step

These two messages may can occur together:

A) PROGRAM TERMINATED BY PRRES, ERROR IN ELS
VAR-COV WITH INDIVIDUAL n (IN INDIVIDUAL RECORD ORDERING)
ESTIMATED TO BE ALGORITHMICALLY SINGULAR

B) MESSAGE ISSUED WHEN CONPAR CALLED WITH ICALL=3

Explanation: With the final parameter estimate, the estimated variance-covariance matrix of the observations from individual n is algorithmically singular. In message B CONPAR refers to the user-supplied subprogram for computing condensed parameter values.

System Action: Program terminates.

User Response: The error can occur only when the final estimate is the initial estimate and only when the Estimation Step is either unconditionally implemented or not implemented. Respond with i-iv, as indicated in section G.3.

These two messages may also occur together:

C) PROGRAM TERMINATED BY PRRES, ERROR IN CONTR
WITH INDIVIDUAL n (IN INDIVIDUAL RECORD ORDERING)
RETURN CODE m

D) MESSAGE ISSUED WHEN CONPAR CALLED WITH ICALL=3

Explanation: CONTR is the user-supplied subprogram for computing the contribution made to the objective function from a given individual's data. It has encountered a fatal error with individual n, and it has issued a return code m. In message D CONPAR refers to the user-supplied subprogram for computing condensed parameter values.

System Action: Program terminates.

User Response: The error can occur only when the final estimate is the initial estimate and only when the Estimation Step is either unconditionally implemented or not implemented. Respond with i-iv, as indicated in section G.3. Response should be appropriate for return code m.

FIGURES

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      A=EXP(-THETA(2)*DATREC(2))
      B=EXP(-THETA(1)*DATREC(2))
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DATREC(1)*THETA(1))/(THETA(3)*C))*D
      G(1)=1.
      RETURN
      END
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    0   1
LABL     DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
STRC        3    1                   1
THCN        1
THTA          1.7      .102       29.
LOWR           .4      .025       10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0 240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

```
NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM)    DOUBLE PRECISION NONMEM    VERSION III LEVEL 1.0
DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER

PROBLEM NO.  1
SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT

NO. OF DATA RECS IN DATA SET:   10
NO. OF DATA ITEMS IN DATA SET:   3
DEP VARIABLE IS DATA ITEM NO.:   3

LABELS TO BE USED FOR ITEMS APPEARING
       IN TABLES AND SCATTERPLOTS ARE:
DOSE    TIME      CP    PRED    RES     WRES

FORMAT FOR DATA IS:
(3F10.0)

TOT. NO. OF OBS RECS:      10
TOT. NO. OF INDIVIDUALS:   10

LENGTH OF THETA:  3

OMEGA HAS SIMPLE DIAGONAL FORM WITH DIMENSION:  1

INITIAL ESTIMATE OF THETA:
LOWER BOUND    INITIAL EST    UPPER BOUND
 0.4000e+00     0.1700e+01     0.7000e+01
 0.2500e-01     0.1020e+00     0.4000e+00
 0.1000e+02     0.2900e+02     0.8000e+02

ESTIMATION STEP OMITTED:    NO
NO. OF FUNCT. EVALS. ALLOWED:  240
NO. OF SIG. FIGURES REQUIRED:    4
INTERMEDIATE PRINTOUT:   YES
CONVERGENCE REPEATED:     NO
MSF OUTPUT:               NO

COVARIANCE STEP OMITTED:    NO
EIGENVLS. PRINTED:    NO
SPECIAL COMPUTATION:  NO

TABLES STEP OMITTED:    NO
NO. OF TABLES:       1
TABLES PRINTED:    YES
TABLES FILE USED:   NO

USER CHOSEN DATA ITEMS FOR TABLE  1,
IN THE ORDER THEY WILL APPEAR IN THE TABLE, ARE:
TIME

SCATTERPLOT STEP OMITTED:    NO
NO. OF PAIRS OF ITEMS GENERATING
        FAMILIES OF SCATTERPLOTS:  4
```

Fig. 3a

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ITEMS TO BE SCATTERED ARE:     TIME       CP
ITEMS TO BE SCATTERED ARE:     TIME     PRED
ITEMS TO BE SCATTERED ARE:     TIME      RES
ITEMS TO BE SCATTERED ARE:       CP     PRED
    UNIT SLOPE LINE INCLUDED
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Fig. 3b

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********************************************************************************************************************************
**********                                                                                                          **********
**********                                    INITIAL PARAMETER ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************
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THETA - VECTOR OF FIXED EFFECTS **********

TH 1	TH 2	TH 3
1.70e+00	1.02e-01	2.90e+01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1
ETA1	1.17e+00

Fig. 4

```
MONITORING OF SEARCH:


ITERATION NO.:    0     OBJECTIVE VALUE:  0.1157e+02     NO. OF FUNC. EVALS.: 5
PARAMETER:  0.1000e+00  0.1000e+00  0.1000e+00  0.1000e+00
GRADIENT:   0.2395e+02 -0.2631e+03 -0.6027e+03  0.3695e-04

ITERATION NO.:    2     OBJECTIVE VALUE:  0.9807e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1102e+00  0.1059e+00  0.1031e+00  0.9106e-01
GRADIENT:   0.1051e+03 -0.3883e+02 -0.3453e+03 -0.2402e+01

ITERATION NO.:    4     OBJECTIVE VALUE:  0.9577e+01     NO. OF FUNC. EVALS.: 7
PARAMETER:  0.1153e+00  0.9850e-01  0.1079e+00  0.7942e-01
GRADIENT:   0.9697e+02 -0.6965e+02 -0.2652e+03 -0.6587e+02

ITERATION NO.:    6     OBJECTIVE VALUE:  0.8943e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1098e+00  0.9997e-01  0.1085e+00  0.8684e-01
GRADIENT:   0.4124e+01 -0.5664e+00 -0.1038e+02 -0.4515e+01

ITERATION NO.:    8     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1097e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   0.5923e-01  0.4162e-01 -0.5070e-01  0.1247e-01

ITERATION NO.:   10     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:  -0.2348e-03  0.4554e-03  0.5354e-03  0.3576e-04

ITERATION NO.:   12     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:  -0.5436e-05  0.0000e+00 -0.2194e-05  0.0000e+00

ITERATION NO.:   14     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 9
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   0.1359e-04 -0.2861e-04 -0.6857e-04 -0.6557e-05

ITERATION NO.:   16     OBJECTIVE VALUE:  0.8940e+01     NO. OF FUNC. EVALS.: 1
PARAMETER:  0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:  -0.1087e-05  0.2384e-05 -0.2194e-05  0.0000e+00

MINIMIZATION ROUTINE SUCCESSFULLY TERMINATED
NO. OF FUNCTION EVALUATIONS USED:  114
NO. OF SIG. DIGITS IN FINAL EST.:  8.5
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Fig. 5

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MINIMUM VALUE OF OBJECTIVE FUNCTION

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8.940

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Fig. 6

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********************************************************************************************************************************
**********                                                                                                          **********
**********                                      FINAL PARAMETER ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************


THETA - VECTOR OF FIXED EFFECTS  **********

           TH 1      TH 2      TH 3

        1.94e+00  1.02e-01  3.20e+01


OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  ********

           ETA1

ETA1     8.99e-01
```

Fig. 7

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STANDARD ERROR OF ESTIMATE

THETA - VECTOR OF FIXED EFFECTS ******** **********

TH 1	TH 2	TH 3
6.28e-01	7.37e-03	1.25e+00

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ******

	ETA1
ETA1	5.45e-01

Fig. 8

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COVARIANCE MATRIX OF ESTIMATE

	TH 1	TH 2	TH 3	OM11
TH 1	3.95e-01			
TH 2	-3.37e-03	5.43e-05		
TH 3	4.91e-01	-7.90e-03	1.57e+00	
OM11	-1.53e-01	2.64e-03	-4.56e-01	2.97e-01

Fig. 9

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CORRELATION MATRIX OF ESTIMATE

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****

	TH 1	TH 2	TH 3	OM11
TH 1	1.00e+00			
TH 2	-7.27e-01	1.00e+00		
TH 3	6.24e-01	-8.55e-01	1.00e+00	
OM11	-4.48e-01	6.59e-01	-6.67e-01	1.00e+00

Fig. 10

Fig. 11

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************************************************************************************************************
********************                                                                   *********************
********************                INVERSE COVARIANCE MATRIX OF ESTIMATE               *********************
********************                                                                   *********************
************************************************************************************************************
```

	TH 1	TH 2	TH 3	OM11
TH 1	5.40e+00			
TH 2	3.42e+02	9.41e+04		
TH 3	-7.86e-02	3.14e+02	2.55e+00	
OM11	-3.83e-01	-1.80e+02	1.08e+00	6.44e+00

TABLES OF DATA AND PREDICTIONS

Fig. 12

TABLE NO. 1

LINE NO.	TIME	CP	PRED	RES	WRES
1	2.70e-01	1.71e+00	4.02e+00	-2.31e+00	-2.43e+00
2	5.20e-01	7.91e+00	6.16e+00	1.75e+00	1.85e+00
3	1.00e+00	8.31e+00	8.01e+00	2.98e-01	3.15e-01
4	1.92e+00	8.33e+00	8.42e+00	-9.15e-02	-9.65e-02
5	3.50e+00	6.85e+00	7.38e+00	-5.26e-01	-5.55e-01
6	5.02e+00	6.08e+00	6.33e+00	-2.49e-01	-2.63e-01
7	7.03e+00	5.40e+00	5.16e+00	2.40e-01	2.53e-01
8	9.00e+00	4.55e+00	4.22e+00	3.27e-01	3.45e-01
9	1.20e+01	3.01e+00	3.11e+00	-1.03e-01	-1.08e-01
10	2.43e+01	9.00e-01	8.91e-01	8.82e-03	9.29e-03

Fig. 13

Fig. 14

Fig. 15

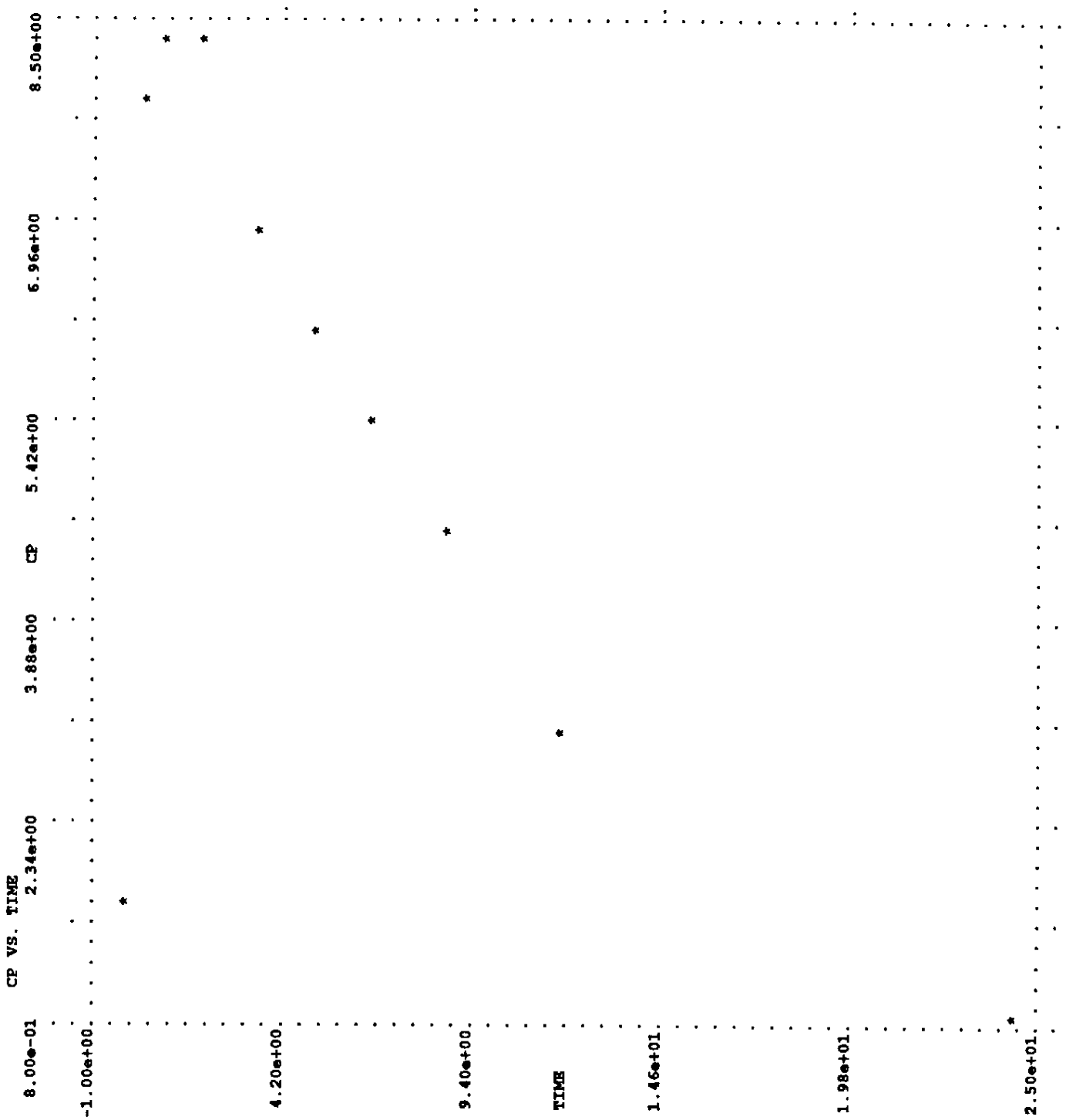

CP VS. TIME
8.50e+00
6.96e+00
5.42e+00
3.88e+00
2.34e+00
8.00e-01
CP
-1.00e+00
4.20e+00
9.40e+00
1.46e+01
1.98e+01
2.50e+01
TIME

Fig. 16

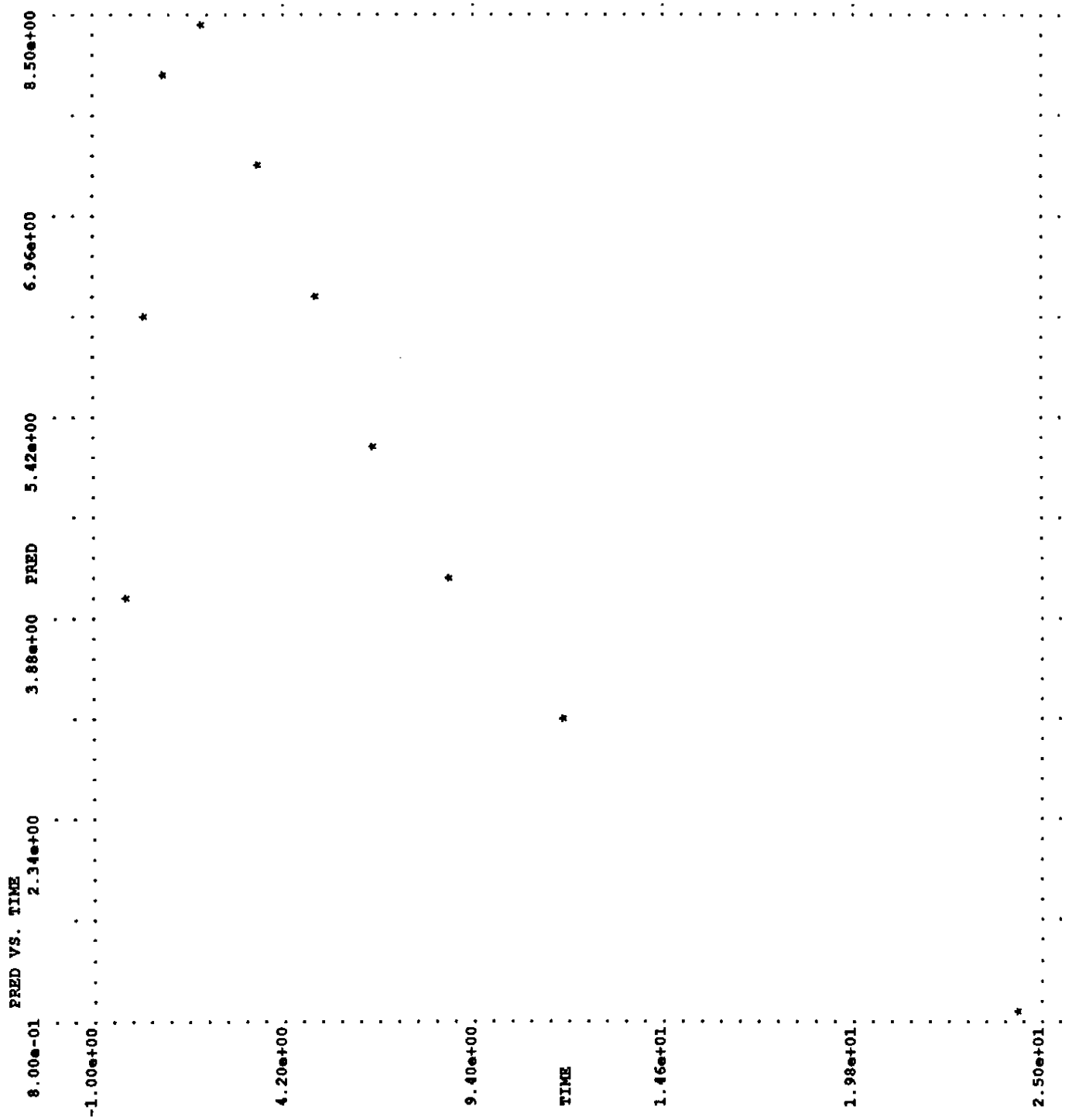

PRED VS. TIME
8.00e-01
2.34e+00
3.88e+00
PRED
5.42e+00
6.96e+00
8.50e+00
-1.00e+00
4.20e+00
9.40e+00
TIME
1.46e+01
1.98e+01
2.50e+01

Fig. 17

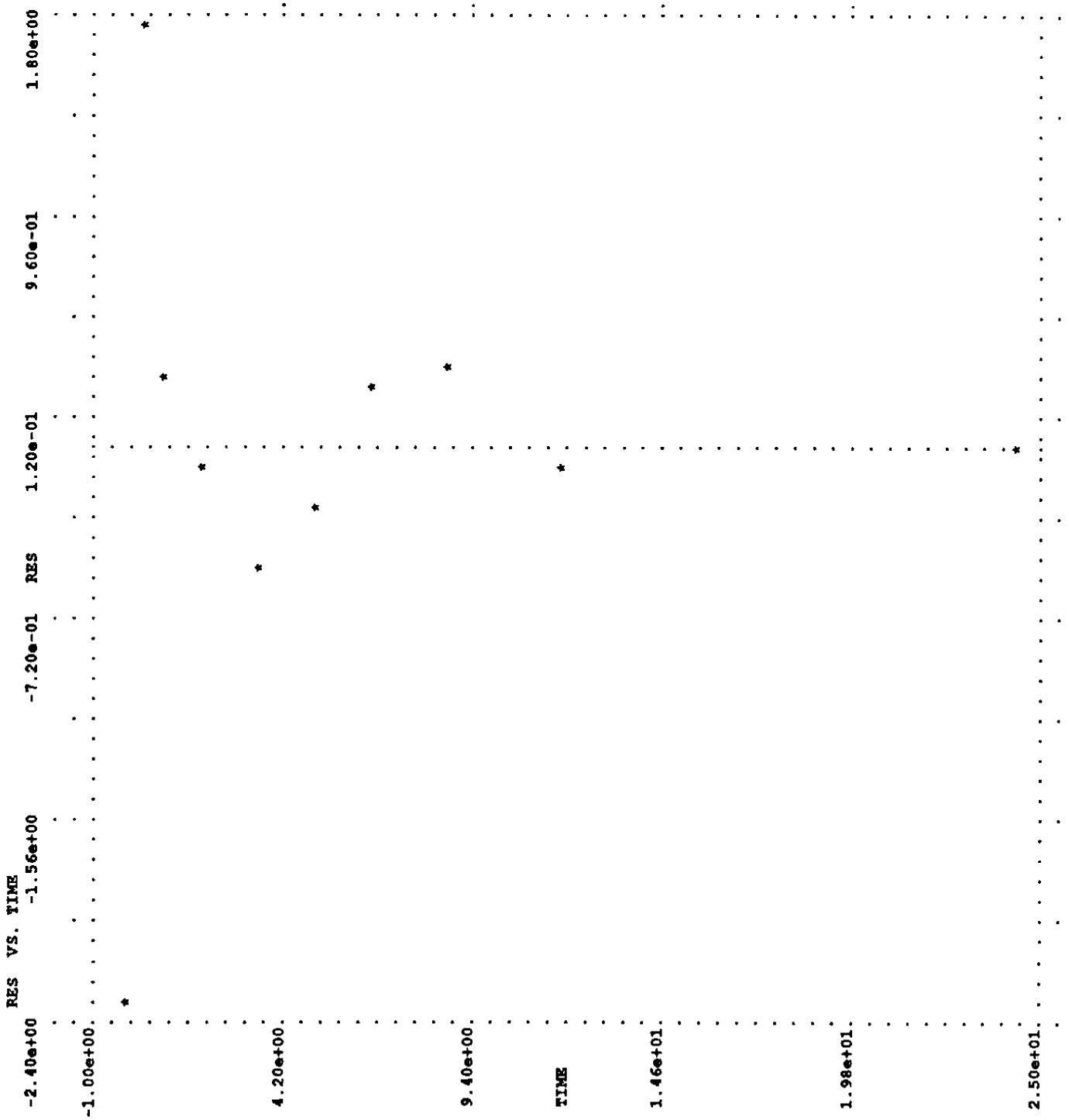
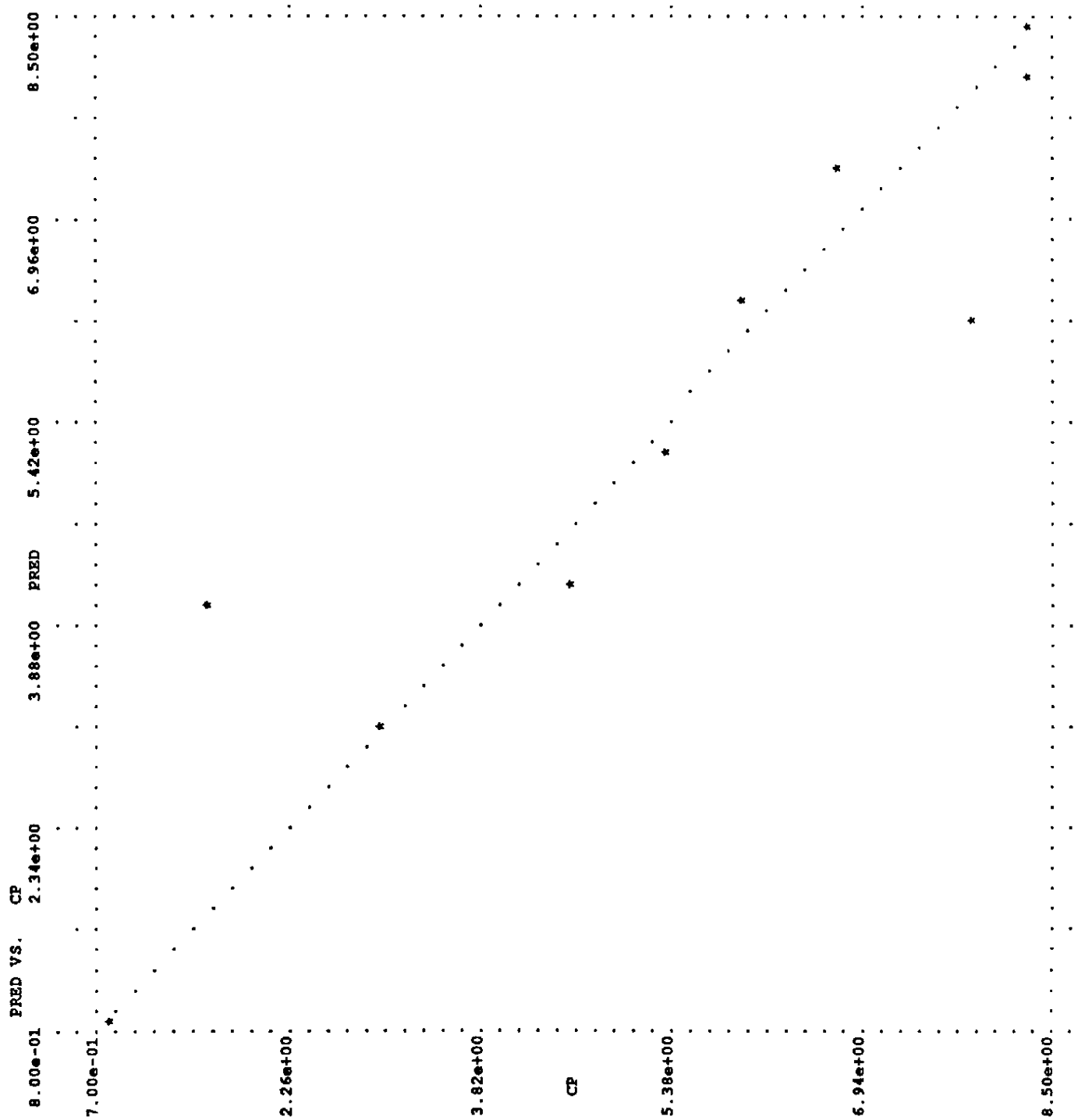

RES VS. TIME
-2.40e+00
-1.56e+00
-7.20e-01
1.20e-01
9.60e-01
1.80e+00
RES
-1.00e+00
4.20e+00
9.40e+00
1.46e+01
1.98e+01
2.50e+01
TIME

Fig. 18


PRED VS. CP
8.00e-01
2.34e+00
3.88e+00
5.42e+00
6.96e+00
8.50e+00
PRED
7.00e-01
2.26e+00
3.82e+00
5.38e+00
6.94e+00
8.50e+00
CP

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
C                                          COMPUTED VALUES
C
C     C=CONCENTRATION IN PLASMA AT CURRENT TIME (MG/L)
C     DO=DOSE IN DEPOT AT CURRENT TIME (MG)
C     DELTA=INCREMENTAL DIFFERENCE IN TIME FROM PREVIOUS TIME
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,DO,A,B,BA,C
C
      IF (NEWIND.NE.0) GO TO 10
C                                          INITIALIZE RECURSION
      C=0.
      TIME=0.
      DO=DATREC(1)
C                                          COMPUTE TIME INCREMENT
   10 DELTA=DATREC(2)-TIME
C                                          COMPUTE EXPONENTIALS
      A=EXP(-THETA(2)*DELTA)
      B=EXP(-THETA(1)*DELTA)
C                                          GET BATEMAN VALUE
      CALL BATE (DO,DELTA,THETA(1),THETA(2),THETA(3),A,B,BA)
C                                          UPDATE C AND DO
      C=BA+C*A
      DO=DO*B
C                                          UPDATE TIME
      TIME=DATREC(2)
C                                          SET OUTPUTS
      F=C
      G(1)=1.
      RETURN
      END
```

```
      SUBROUTINE BATE (DO,DELTA,KA,KD,VL,A,B,BA)
C
C                                          INPUTS
C     DO=DOSE
C     DELTA=TIME
C     KA=MEAN ABSORPTION RATE
C     KD=MEAN ELIMINATION RATE
C     VL=VOLUME OF DISTRIBUTION
C     A=EXP(-KD*DELTA)
C     B=EXP(-KA*DELTA)
C                                          OUTPUTS
C     BA=BATEMAN VALUE
C
      DOUBLE PRECISION DO,KA,KD,VL,A,B,BA,C,D
C
      C=KA-KD
      D=A-B
      BA=DO*KA/(VL*C)*D
      RETURN
      END
```

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     INDXS(1)=DOSE (MG)
C     INDXS(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      DO=DATREC(INDXS(1))
      TIME=DATREC(INDXS(2))
      A=EXP(-THETA(2)*TIME)
      B=EXP(-THETA(1)*TIME)
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DO*THETA(1))/(THETA(3)*C))*D
      G(1)=1.
      RETURN
      END
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    2    1
INDX        1    2
LABL     DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
STRC        3    1                    1
THCN        1
THTA          1.7      .102       29.
LOWR           .4      .025       10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0 240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                    1
```

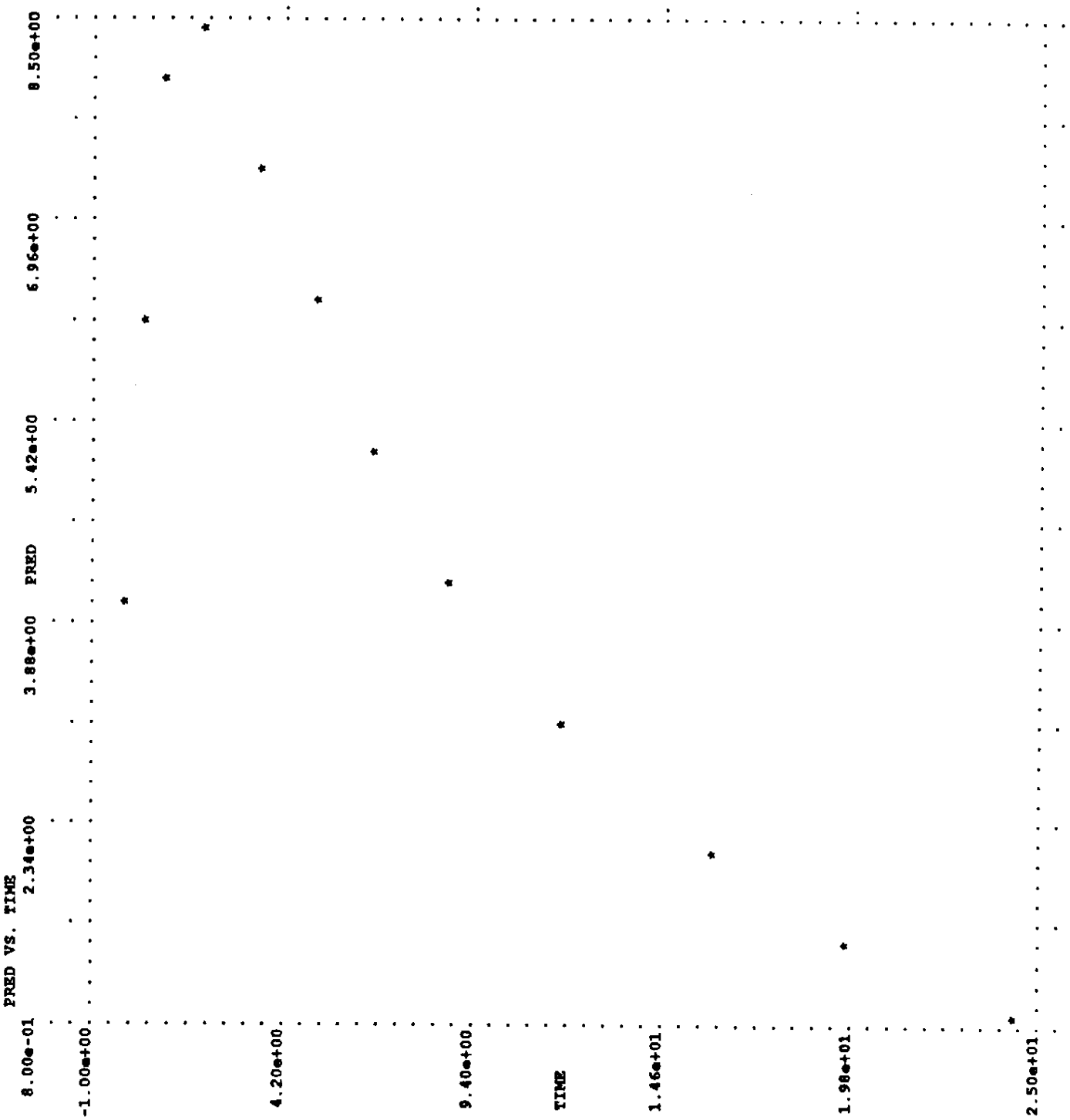
```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    2    1
INDX        2    1
LABL     TIME      DOSE        CP
FORM
(3F10.0)
        .27          320        1.71
        .52          320        7.91
       1.0           320        8.31
       1.92          320        8.33
       3.5           320        6.85
       5.02          320        6.08
       7.03          320        5.4
       9.0           320        4.55
      12.0           320        3.01
      24.3           320         .90
STRC         3    1                    1
THCN         1
THTA           1.7      .102       29.
LOWR            .4      .025       10.
UPPR           7.        .4        80.
DIAG    2
ESTM         0 240    4    2
COVR         0
TABL         0    1
TABL         1    1
SCAT         0    4
SCAT         1    3
SCAT         1    4
SCAT         1    5
SCAT         3    4                    1
```

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      IF (ICALL.EQ.0) RETURN
      IF (ICALL.EQ.1) THEN
C                              INPUT DOSE
      READ (5,5) DOSE
    5 FORMAT (F10.0)
      RETURN
C
      ELSEIF (ICALL.EQ.2) THEN
C                                COMPUTE F AND G
      A=EXP(-THETA(2)*DATREC(1))
      B=EXP(-THETA(1)*DATREC(1))
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DOSE*THETA(1))/(THETA(3)*C))*D
      G(1)=1.
      RETURN
C
      ENDIF
      END
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    2
ITEM        0    2   0    0    1
LABL     TIME       CP
FORM
(2F10.0)
        .27        1.71
        .52        7.91
       1.0         8.31
       1.92        8.33
       3.5         6.85
       5.02        6.08
       7.03        5.4
       9.0         4.55
      12.0         3.01
      24.3          .90
STRC         3    1                    1
THCN         1
THTA           1.7      .102       29.
LOWR            .4      .025       10.
UPPR           7.        .4        80.
DIAG    2
ESTM         0 240    4    2
COVR         0
TABL         0    1
TABL         1    1
SCAT         0    4
SCAT         1    2
SCAT         1    3
SCAT         1    4
SCAT         2    3                    1
       320.
```

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  12    5
ITEM        5    3   4    0   1
LABL     DOSE     TIME        CP      MDV       ID
FORM
(5F10.0)
        320         .27        1.71          0          1
        320         .52        7.91          0          2
        320        1.0         8.31          0          3
        320        1.92        8.33          0          4
        320        3.5         6.85          0          5
        320        5.02        6.08          0          6
        320        7.03        5.4           0          7
        320        9.0         4.55          0          8
        320       12.0         3.01          0          9
        320       16.0                       1          9
        320       20.0                       1          9
        320       24.3          .90          0         10
STRC        3    1                    1
THCN        1
THTA          1.7      .102      29.
LOWR           .4      .025      10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0 240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    6
SCAT        2    7
SCAT        3    6                    1
```

Fig. 27


PRED VS. TIME
8.00e-01
2.34e+00
3.88e+00
PRED
5.42e+00
6.96e+00
8.50e+00
-1.00e+00
4.20e+00
9.40e+00
TIME
1.46e+01
1.98e+01
2.50e+01

```
FILE    FILESTREAM
PROB    SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA       0    0  10    3
ITEM       0    3   0    0   1
LABL    DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
STRC        3    1                   1
THCN        1
THTA          1.7      .102       29.
LOWR           .4      .025       10.
UPPR          7.        .4        80.
DIAG    2
ESTM        0   50    4    2         1
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

Fig. 29

MSFO MSF1
****

```
MONITORING OF SEARCH:


ITERATION NO.:    0     OBJECTIVE VALUE:  0.1157e+02     NO. OF FUNC. EVALS.: 5
PARAMETER:  0.1000e+00  0.1000e+00  0.1000e+00  0.1000e+00
GRADIENT:   0.2395e+02 -0.2631e+03 -0.6027e+03  0.3695e-04

ITERATION NO.:    2     OBJECTIVE VALUE:  0.9807e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1102e+00  0.1059e+00  0.1031e+00  0.9106e-01
GRADIENT:   0.1051e+03 -0.3883e+02 -0.3453e+03 -0.2402e+01

ITERATION NO.:    4     OBJECTIVE VALUE:  0.9577e+01     NO. OF FUNC. EVALS.: 7
PARAMETER:  0.1153e+00  0.9850e-01  0.1079e+00  0.7942e-01
GRADIENT:   0.9697e+02 -0.6965e+02 -0.2652e+03 -0.6587e+02

ITERATION NO.:    6     OBJECTIVE VALUE:  0.8943e+01     NO. OF FUNC. EVALS.: 6
PARAMETER:  0.1098e+00  0.9997e-01  0.1085e+00  0.8684e-01
GRADIENT:   0.4124e+01 -0.5664e+00 -0.1038e+02 -0.4515e+01

MINIMIZATION ROUTINE TERMINATED
DUE TO MAX. NO. OF FUNCTION EVALUATIONS EXCEEDED
NO. OF FUNCTION EVALUATIONS USED:   51
NO. OF SIG. DIGITS IN FINAL EST.:  1.7
```

Fig. 30

```
FILE     FILESTREAM
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    0    1
LABL     DOSE     TIME        CP
FORM
(3F10.0)
        320         .27        1.71
        320         .52        7.91
        320        1.0         8.31
        320        1.92        8.33
        320        3.5         6.85
        320        5.02        6.08
        320        7.03        5.4
        320        9.0         4.55
        320       12.0         3.01
        320       24.3          .90
FIND
ESTM        0 150    4    2         1
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

```
MSFO     MSF2
MSFI     MSF1
****
```

```
MONITORING OF SEARCH:


ITERATION NO.:     0      OBJECTIVE VALUE:  0.8943e+01      NO. OF FUNC. EVALS.: 5
PARAMETER:   0.1098e+00  0.9997e-01  0.1085e+00  0.8684e-01
GRADIENT:    0.4124e+01 -0.5664e+00 -0.1038e+02 -0.4515e+01

ITERATION NO.:     2      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 6
PARAMETER:   0.1097e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:    0.5923e-01  0.4162e-01 -0.5070e-01  0.1247e-01

ITERATION NO.:     4      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 6
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   -0.2348e-03  0.4554e-03  0.5354e-03  0.3576e-04

ITERATION NO.:     6      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 6
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   -0.5436e-05  0.0000e+00 -0.2194e-05  0.0000e+00

ITERATION NO.:     8      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 9
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:    0.1359e-04 -0.2861e-04 -0.6857e-04 -0.6557e-05

ITERATION NO.:    10      OBJECTIVE VALUE:  0.8940e+01      NO. OF FUNC. EVALS.: 1
PARAMETER:   0.1096e+00  0.9978e-01  0.1087e+00  0.8768e-01
GRADIENT:   -0.1087e-05  0.2384e-05 -0.2194e-05  0.0000e+00

MINIMIZATION ROUTINE SUCCESSFULLY TERMINATED
NO. OF FUNCTION EVALUATIONS USED:    68
NO. OF SIG. DIGITS IN FINAL EST.:  8.5
```

Fig. 33

```
FILE     NULL
PROB     SIMPLE NONLINEAR REGRESSION OF CP VS TIME DATA FROM ONE SUBJECT
DATA        0    0  10    3
ITEM        0    3   0    0   1
LABL     DOSE     TIME       CP
FORM
(3F10.0)
        320         .27       1.71
        320         .52       7.91
        320        1.0        8.31
        320        1.92       8.33
        320        3.5        6.85
        320        5.02       6.08
        320        7.03       5.4
        320        9.0        4.55
        320       12.0        3.01
        320       24.3         .90
STRC        3    1                   1
THCN        1
THTA                    .102      29.
LOWR             .4     .025      10.
UPPR           7.       .4        80.
DIAG    2
ESTM        0  240    4    2
COVR        0
TABL        0    1
TABL        1    2
SCAT        0    4
SCAT        2    3
SCAT        2    4
SCAT        2    5
SCAT        3    4                   1
```

****
****
****
****

INITIAL PARAMETER ESTIMATE

****
****
****
****

THETA - VECTOR OF FIXED EFFECTS **********

TH 1	TH 2	TH 3
1.50e+00	1.02e-01	2.90e+01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1
ETA1	1.20e+00

Fig. 35

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     THETA(4)=POWER PARAMETER
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D
C
      A=EXP(-THETA(2)*DATREC(2))
      B=EXP(-THETA(1)*DATREC(2))
      C=THETA(1)-THETA(2)
      D=A-B
      F=((DATREC(1)*THETA(1))/(THETA(3)*C))*D
      G(1)=F**THETA(4)
      RETURN
      END
```

```
FILE     NULL
PROB     NONLINEAR REGRESSION WITH POWER FUNCTION VARIANCE MODEL
DATA        0    0  10    3
ITEM        0    3   0    0   1
LABL     DOSE     TIME       CP
FORM
(3F10.0)
        320         .27       1.71
        320         .52       7.91
        320        1.0        8.31
        320        1.92       8.33
        320        3.5        6.85
        320        5.02       6.08
        320        7.03       5.4
        320        9.0        4.55
        320       12.0        3.01
        320       24.3         .90
STRC         4    1                    1
THCN         1         10
THTA           1.7      .102      29.
LOWR            .4      .025      10.       0.
UPPR           7.       .4        80.       3.
DIAG    2
ESTM         0 240    4    2
COVR         0
TABL         0    1
TABL         1    2
SCAT         0    4
SCAT         2    3
SCAT         2    4
SCAT         2    6
SCAT         3    4                    1
```

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=PROPORTIONALITY CONSTANT
C     THETA(2)=ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=VOLUME OF DISTRIBUTION (LITERS)
C     DATREC(1)=DOSE (MG)
C     DATREC(2)=TIME (HR)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,B,C
C
      B=EXP(-THETA(2)*DATREC(2))
      C=DATREC(1)/THETA(3)*B
      F=C
      IF (DATREC(4).EQ.1.) F=THETA(1)*C
      G(1)=1.-DATREC(4)
      G(2)=DATREC(4)
      RETURN
      END
```

```
FILE     NULL
PROB     NONLINEAR REGRESSION WITH TWO TYPES OF OBSERVATIONS
DATA        0    0  23    4
ITEM        2    3   0    0   1
LABL     DOSE     TIME      CONC      P/S
FORM
(4F10.0)
        160        1.          5.32          0
        160        2.          4.88          0
        160        3.          4.1           0
        160        4.          4.21          0
        160        4.          2.24          1
        160        5.          3.96          0
        160        5.          2.31          1
        160        6.          3.76          0
        160        6.          2.05          1
        160        7.17        3.61          0
        160        7.17        1.91          1
        160        8.          3.40          0
        160        8.          1.90          1
        160        8.78        3.14          0
        160        8.78        1.84          1
        160        9.95        1.67          1
        160       12.00        1.47          1
        160       14.50        1.31          1
        160       15.92        1.17          1
        160       24.33        1.03          0
        160       26.           .89          0
        160       28.           .78          0
        160       32.           .56          0
STRC         3    2                      1
STRC         1    2
THCN         1
THTA           .60       .07     28.1
LOWR           .12       .01      6.0
UPPR          3.0        .40    140.0
BLST    2
ESTM         0 450    4    5
COVR         0
TABL         0    1
TABL         2    2    2    4    1
SCAT         0    8
SCAT         2    3
SCAT         2    3    1    4
SCAT         2    5
SCAT         2    5    1    4
SCAT         2    6
SCAT         2    6    1    4
SCAT         3    5                   1
SCAT         3    5    1    4         1
```

TABLE NO. 1

LINE NO.	P/S	TIME	CONC	PRED	RES	WRES
1	0.00e+00	1.00e+00	5.32e+00	5.09e+00	2.31e-01	1.36e+00
2	0.00e+00	2.00e+00	4.88e+00	4.78e+00	9.79e-02	5.77e-01
3	0.00e+00	3.00e+00	4.10e+00	4.49e+00	-3.94e-01	-2.32e+00
4	0.00e+00	4.00e+00	4.21e+00	4.22e+00	-1.31e-02	-1.19e-01
5	0.00e+00	5.00e+00	3.96e+00	3.97e+00	-8.65e-03	-3.13e-02
6	0.00e+00	6.00e+00	3.76e+00	3.73e+00	3.05e-02	1.64e-01
7	0.00e+00	7.17e+00	3.61e+00	3.47e+00	1.42e-01	8.25e-01
8	0.00e+00	8.00e+00	3.40e+00	3.29e+00	1.06e-01	6.40e-01
9	0.00e+00	8.78e+00	3.14e+00	3.14e+00	2.28e-03	3.30e-02
10	0.00e+00	2.43e+01	1.03e+00	1.19e+00	-1.64e-01	-9.65e-01
11	0.00e+00	2.60e+01	8.90e-01	1.08e+00	-1.86e-01	-1.10e+00
12	0.00e+00	2.80e+01	7.80e-01	9.50e-01	-1.70e-01	-1.00e+00
13	0.00e+00	3.20e+01	5.60e-01	7.41e-01	-1.81e-01	-1.07e+00
14	1.00e+00	4.00e+00	2.24e+00	2.38e+00	-1.44e-01	-2.18e+00
15	1.00e+00	5.00e+00	2.31e+00	2.24e+00	6.95e-02	1.05e+00
16	1.00e+00	6.00e+00	2.05e+00	2.11e+00	-5.55e-02	-8.28e-01
17	1.00e+00	7.17e+00	1.91e+00	1.96e+00	-4.78e-02	-6.81e-01
18	1.00e+00	8.00e+00	1.90e+00	1.86e+00	4.06e-02	6.42e-01
19	1.00e+00	8.78e+00	1.84e+00	1.77e+00	6.86e-02	1.03e+00
20	1.00e+00	9.95e+00	1.67e+00	1.65e+00	2.28e-02	3.43e-01
21	1.00e+00	1.20e+01	1.47e+00	1.45e+00	1.99e-02	2.99e-01
22	1.00e+00	1.45e+01	1.31e+00	1.24e+00	6.86e-02	1.03e+00
23	1.00e+00	1.59e+01	1.17e+00	1.14e+00	3.34e-02	5.03e-01

Fig. 40

Fig. 41

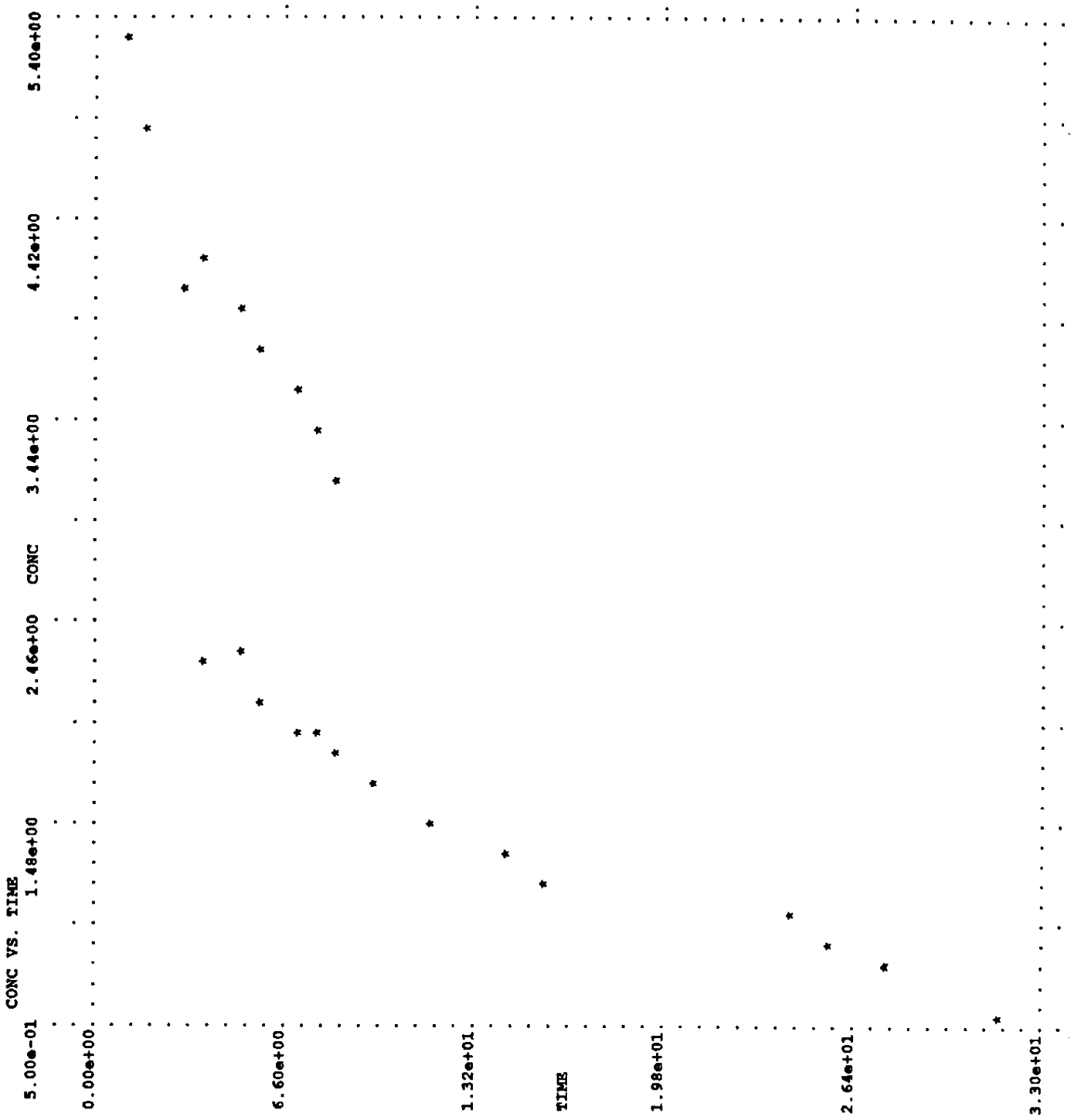

CONC VS. TIME
CONC
TIME
5.00e-01
1.48e+00
2.46e+00
3.44e+00
4.42e+00
5.40e+00
0.00e+00
6.60e+00
1.32e+01
1.98e+01
2.64e+01
3.30e+01

Fig. 42

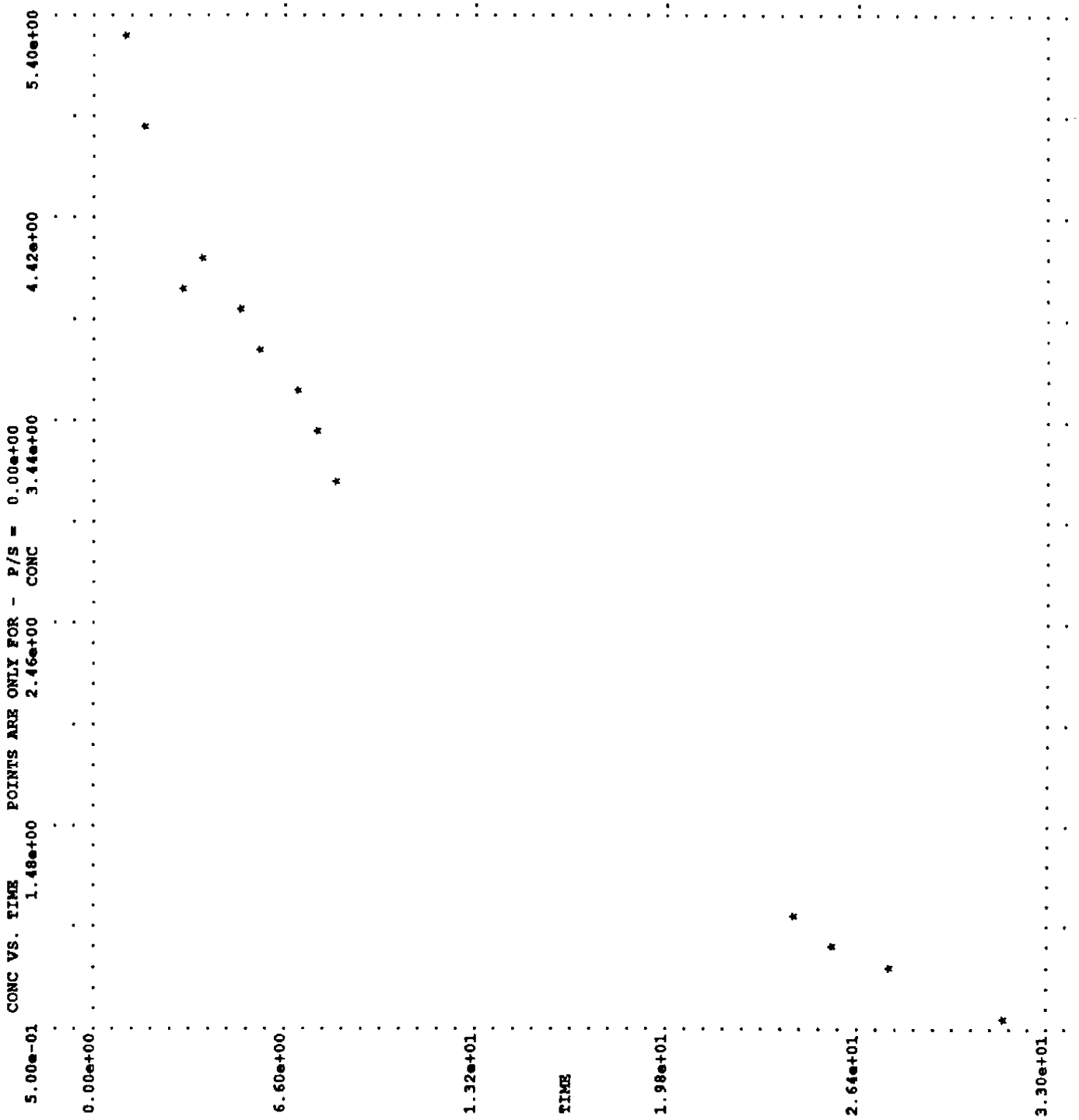

CONC VS. TIME POINTS ARE ONLY FOR - P/S = 0.00e+00
5.00e-01 1.48e+00 2.46e+00 CONC 3.44e+00 4.42e+00 5.40e+00
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 43

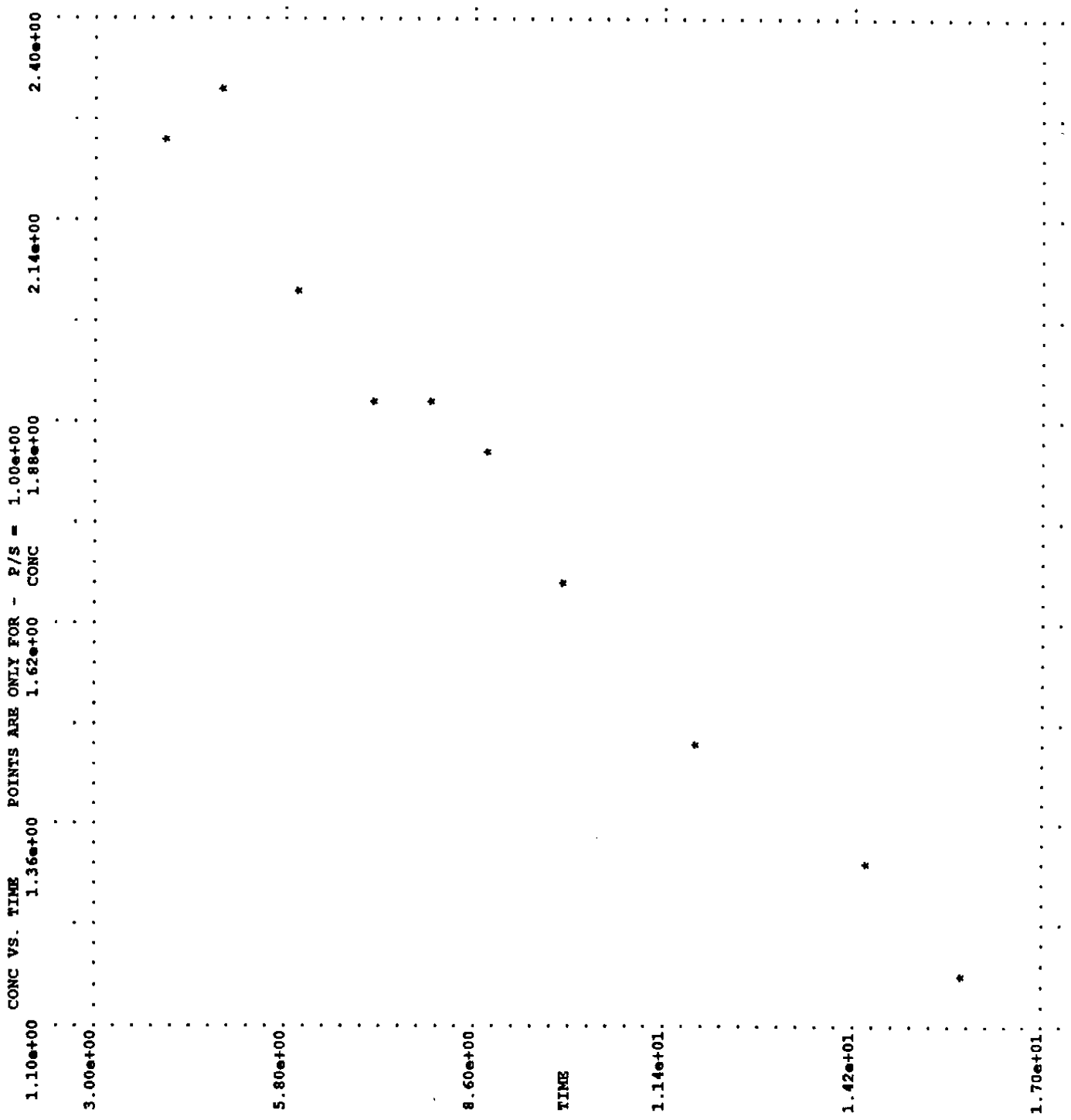

CONC VS. TIME POINTS ARE ONLY FOR - P/S = 1.00e+00
1.10e+00
1.36e+00
1.62e+00
CONC
1.88e+00
2.14e+00
2.40e+00
3.00e+00.
5.80e+00.
8.60e+00.
TIME
1.14e+01.
1.42e+01.
1.70e+01.

Fig. 44

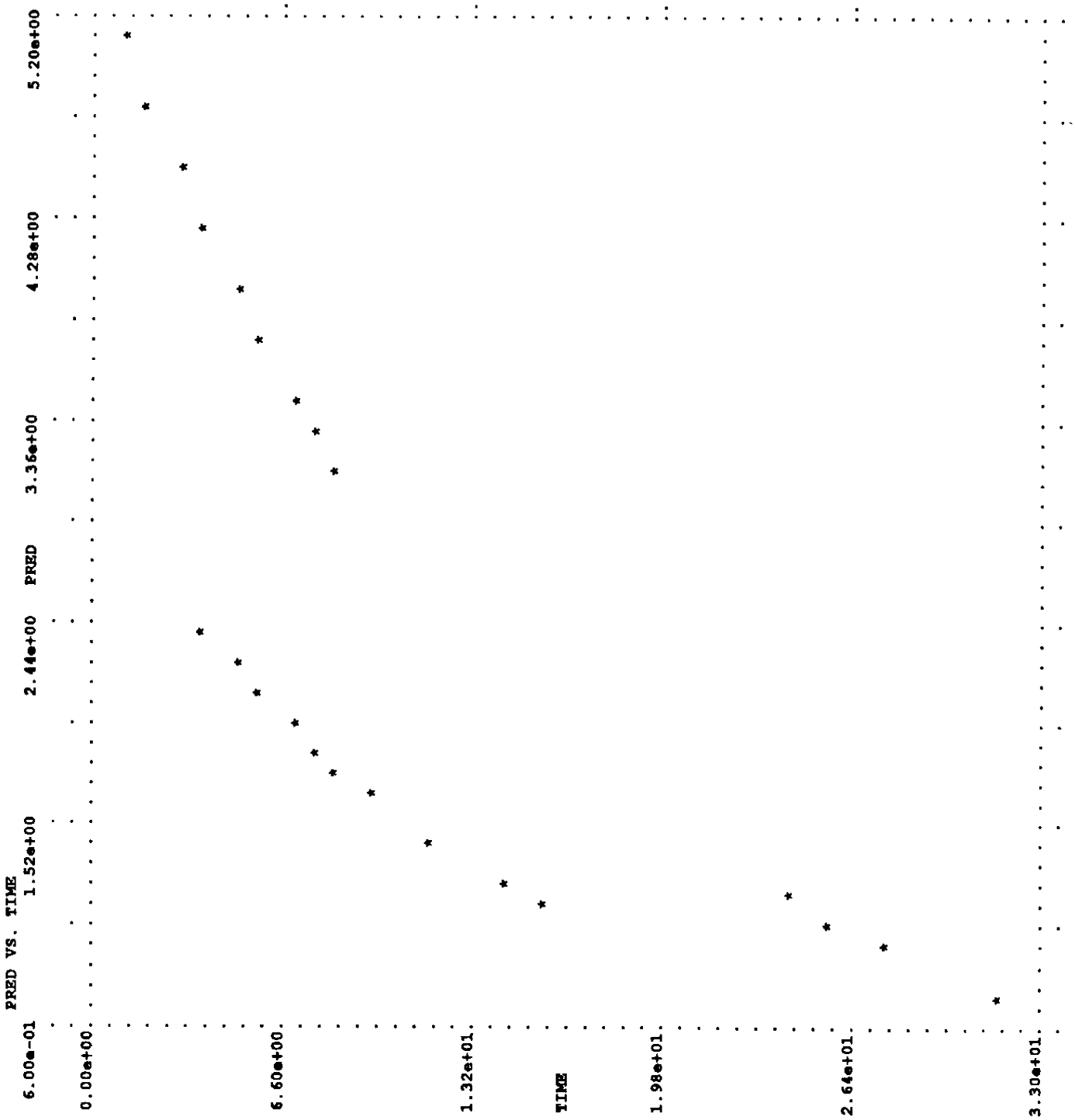

PRED VS. TIME
6.00e-01
1.52e+00
2.44e+00
PRED
3.36e+00
4.28e+00
5.20e+00
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 45

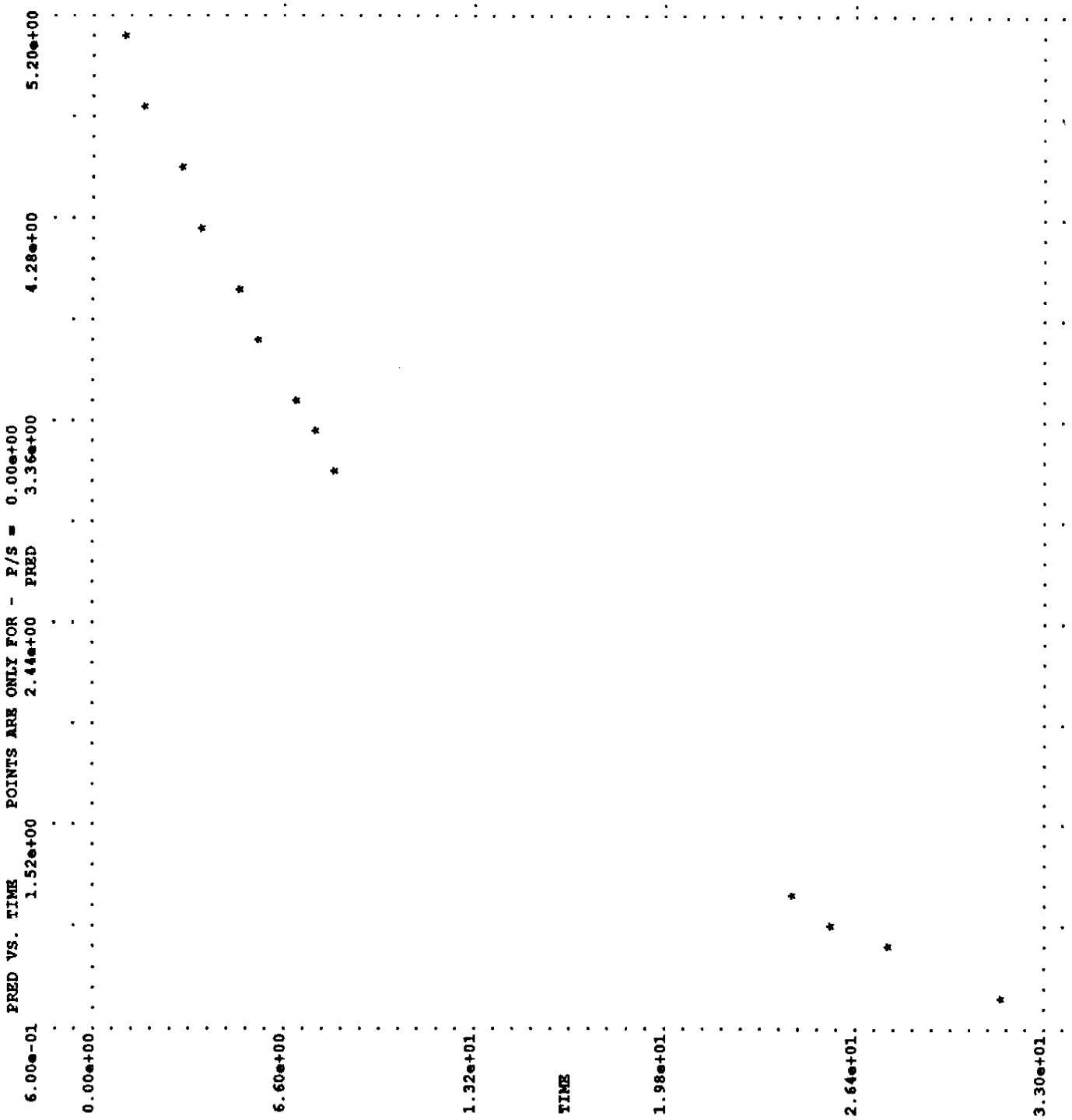

PRED VS. TIME POINTS ARE ONLY FOR - P/S = 0.00e+00
6.00e-01
1.52e+00
2.44e+00
PRED
3.36e+00
4.28e+00
5.20e+00
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 46

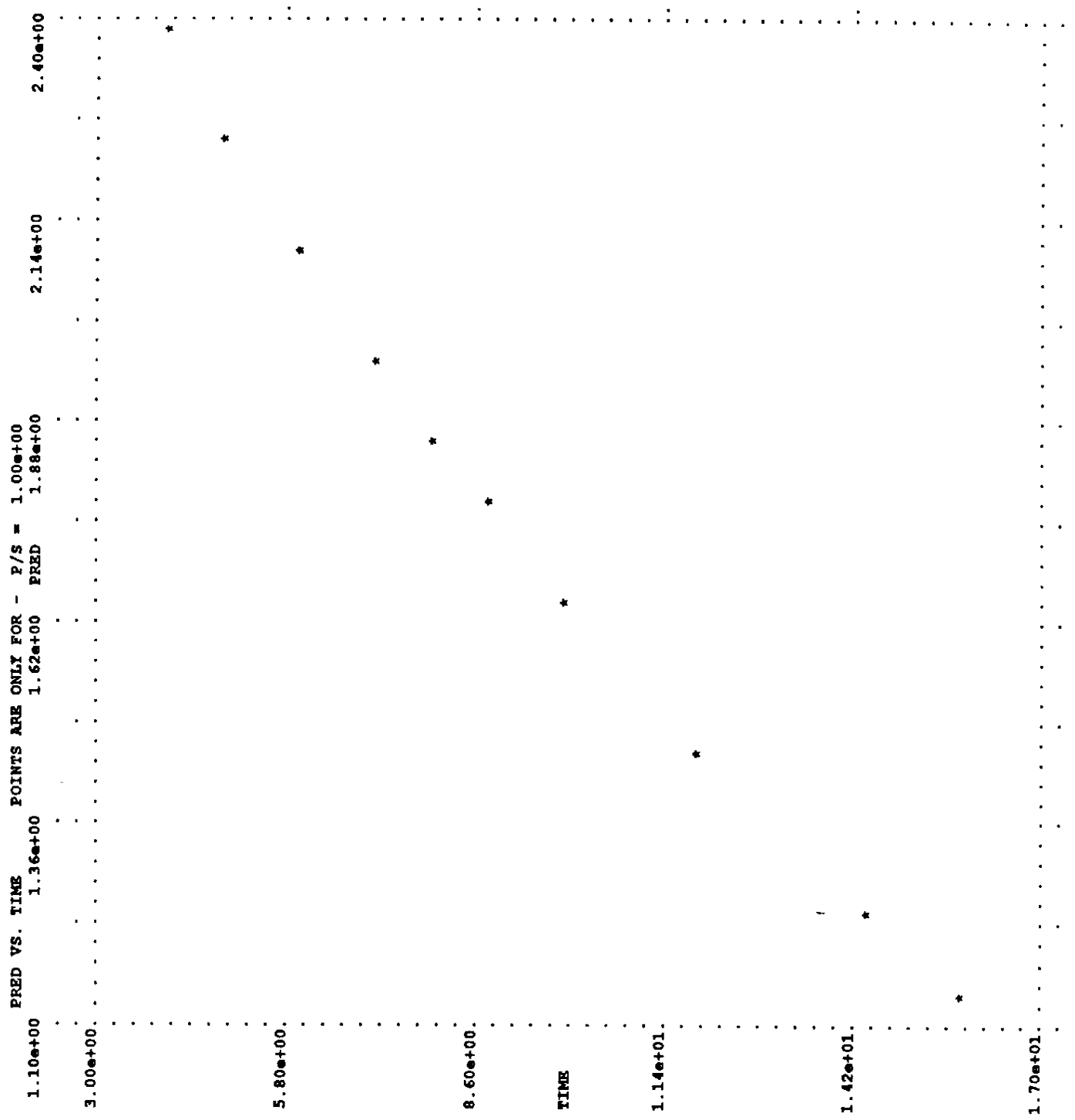

PRED VS. TIME POINTS ARE ONLY FOR - P/S = 1.00e+00
1.10e+00
1.36e+00
1.62e+00
PRED
1.88e+00
2.14e+00
2.40e+00
3.00e+00
5.80e+00
8.60e+00
TIME
1.14e+01
1.42e+01
1.70e+01

Fig. 47

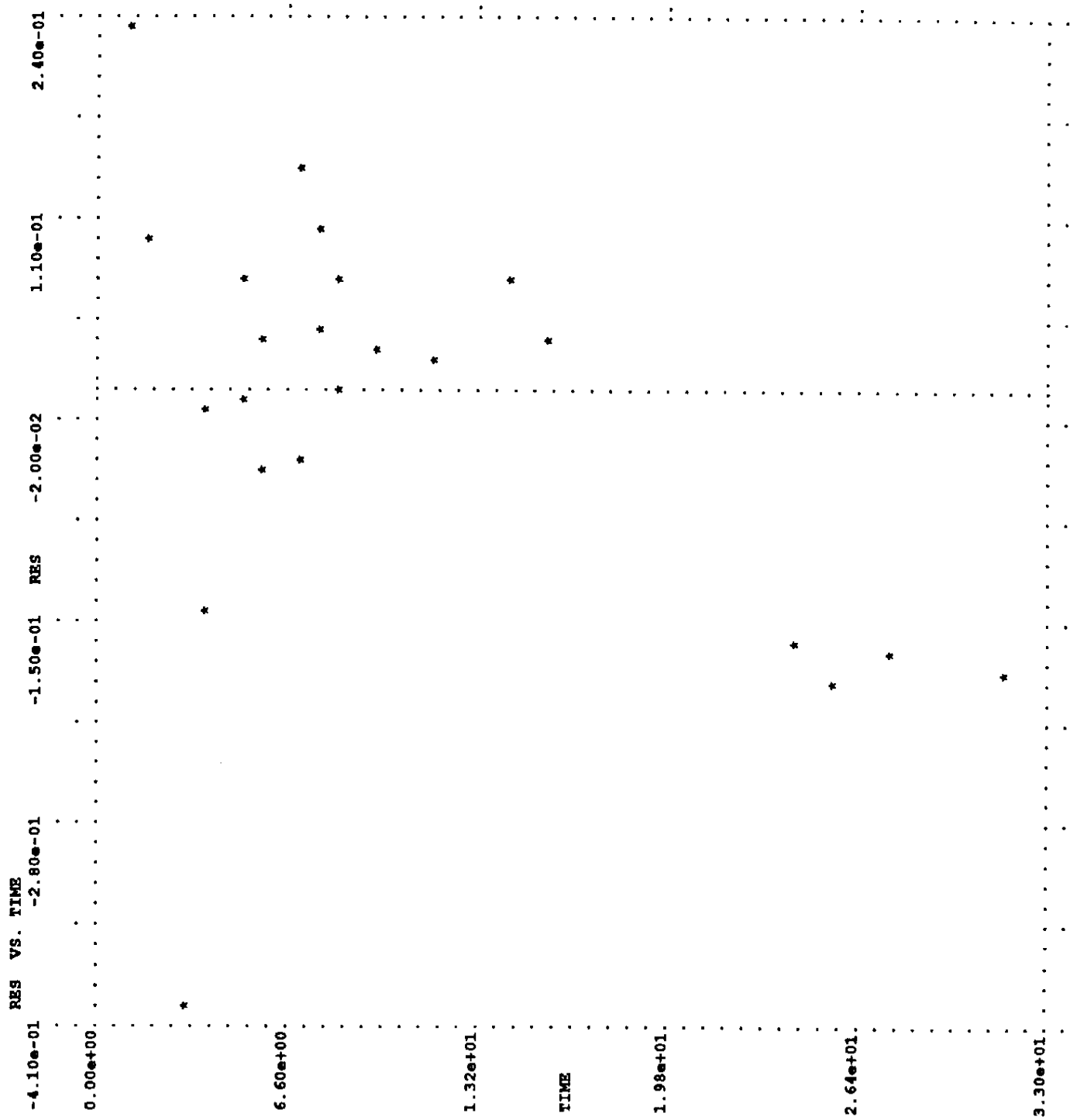

RES VS. TIME
RES
TIME
-4.10e-01
-2.80e-01
-1.50e-01
-2.00e-02
1.10e-01
2.40e-01
0.00e+00
6.60e+00
1.32e+01
1.98e+01
2.64e+01
3.30e+01

Fig. 48

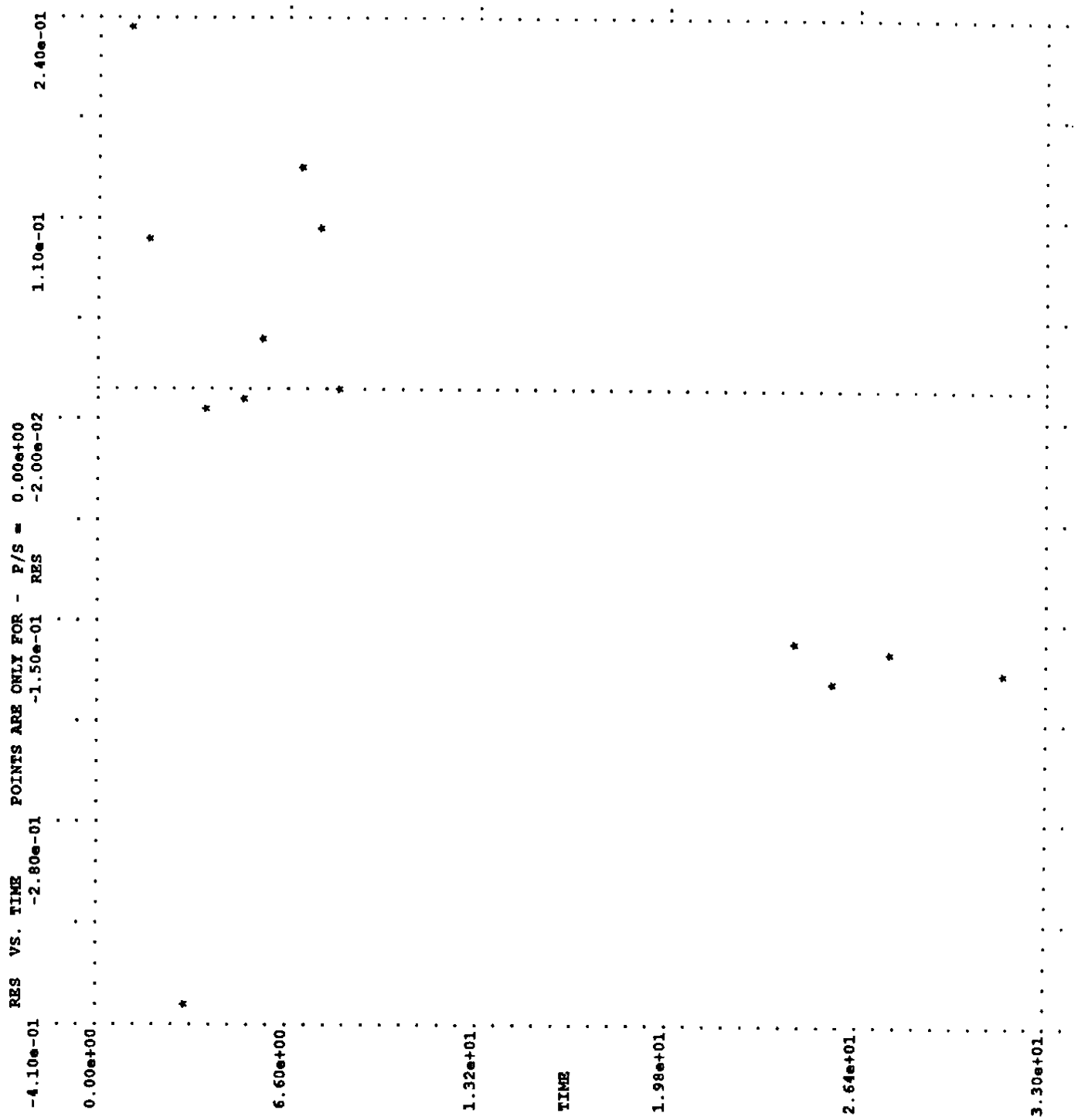

RES VS. TIME POINTS ARE ONLY FOR - P/S = 0.00e+00
-4.10e-01
-2.80e-01
-1.50e-01
RES
-2.00e-02
1.10e-01
2.40e-01
0.00e+00
6.60e+00
1.32e+01
TIME
1.98e+01
2.64e+01
3.30e+01

Fig. 49

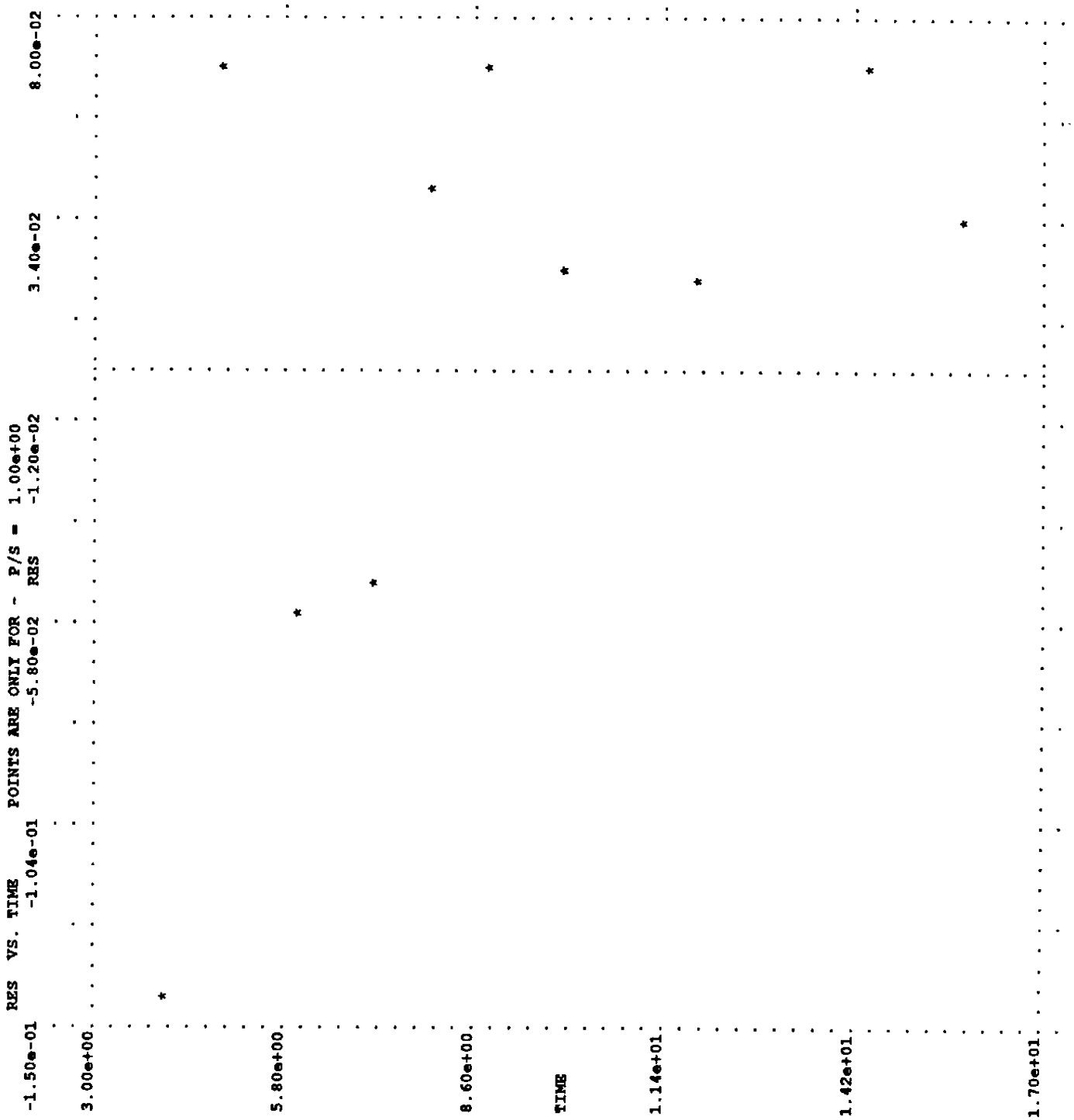

RES VS. TIME POINTS ARE ONLY FOR - P/S = 1.00e+00
-1.50e-01
-1.04e-01
-5.80e-02
RES
-1.20e-02
3.40e-02
8.00e-02
3.00e+00
5.80e+00
8.60e+00
TIME
1.14e+01
1.42e+01
1.70e+01

Fig. 50

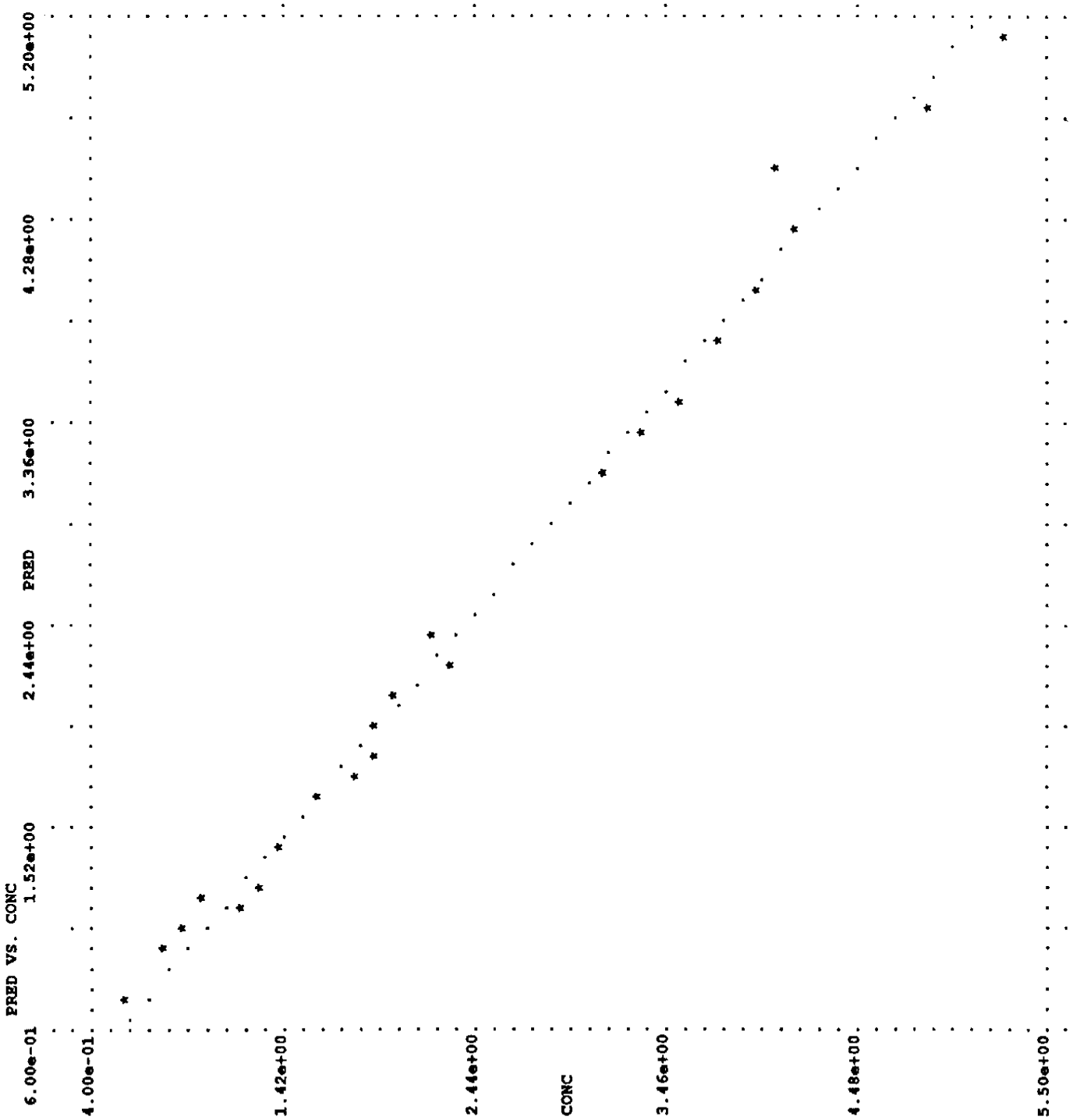

PRED VS. CONC
6.00e-01
4.00e-01
1.52e+00
2.44e+00
PRED
3.36e+00
4.28e+00
5.20e+00
1.42e+00
2.44e+00
CONC
3.46e+00
4.48e+00
5.50e+00

Fig. 51

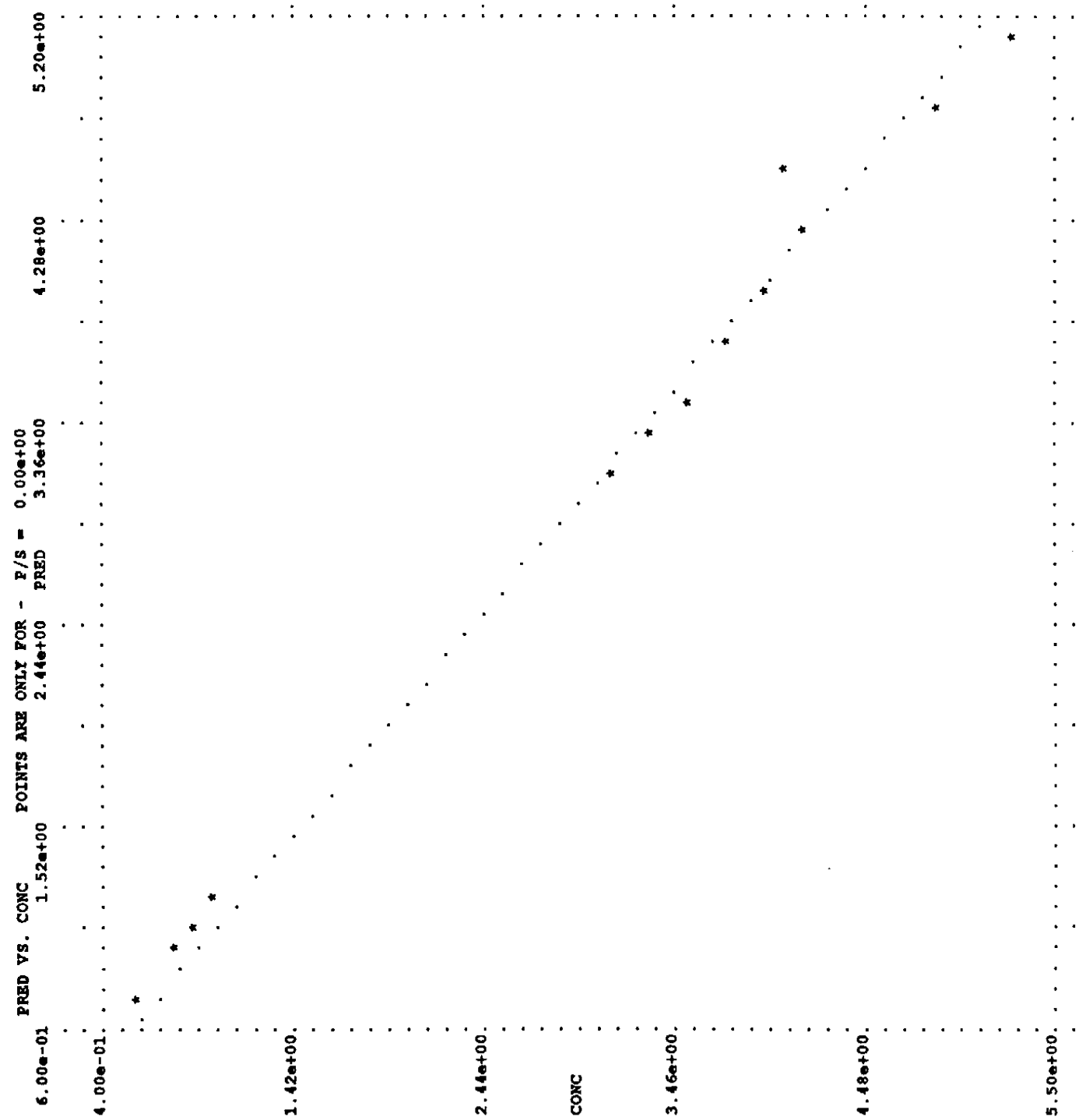
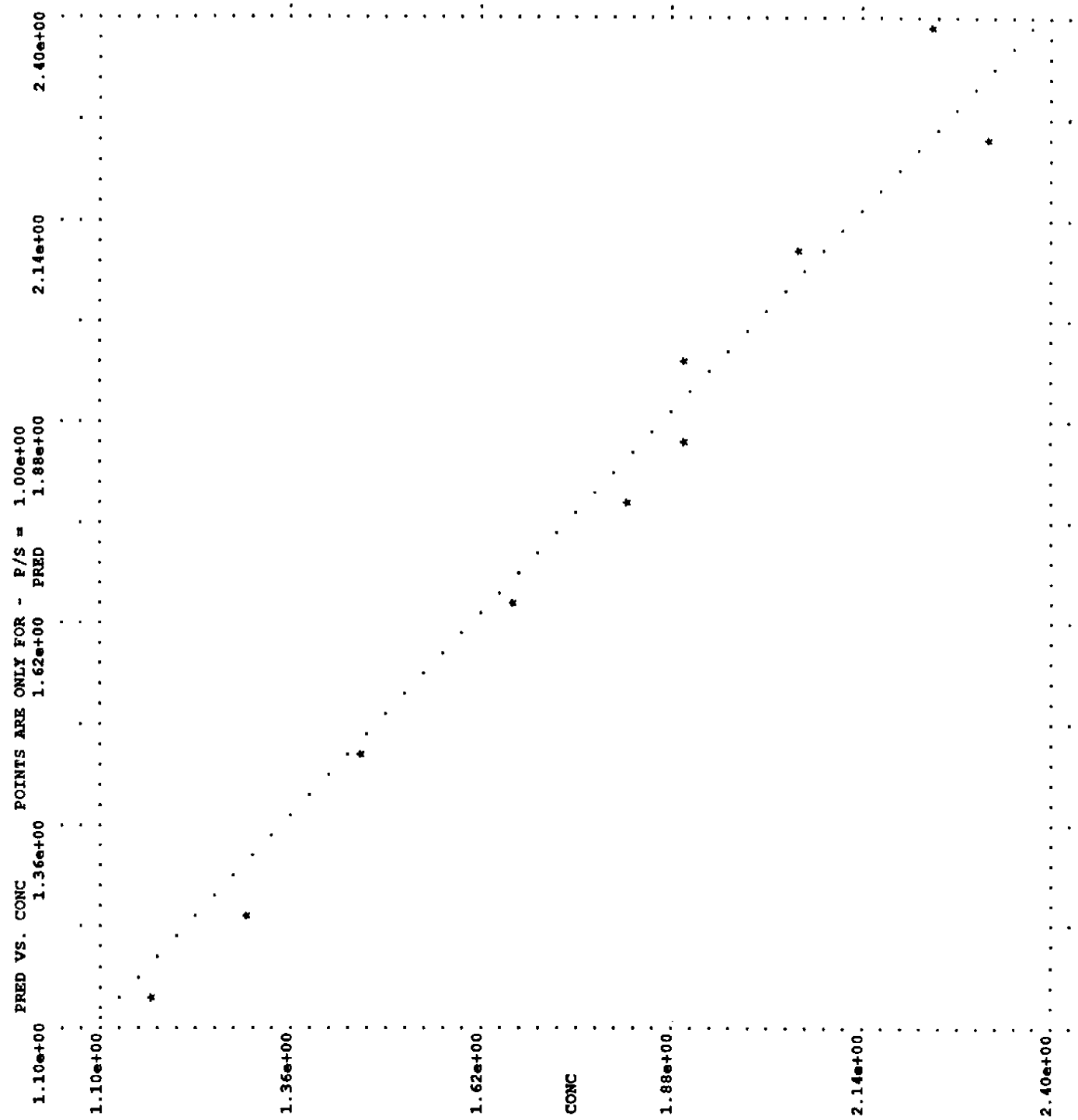

PRED VS. CONC POINTS ARE ONLY FOR - P/S = 0.00e+00
6.00e-01 1.52e+00 2.44e+00 PRED 3.36e+00 4.28e+00 5.20e+00
4.00e-01
1.42e+00
2.44e+00
CONC
3.46e+00
4.48e+00
5.50e+00

Fig. 52


PRED VS. CONC POINTS ARE ONLY FOR - P/S = 1.00e+00
1.10e+00 1.36e+00 1.62e+00 PRED 1.88e+00 2.14e+00 2.40e+00
1.10e+00
1.36e+00
1.62e+00
CONC
1.88e+00
2.14e+00
2.40e+00

```
NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM)    DOUBLE PRECISION NONMEM    VERSION III LEVEL 1.0
DEVELOPED AND PROGRAMMED BY STUART BEAL AND LEWIS SHEINER

PROBLEM NO.  1
NONLINEAR REGRESSION WITH TWO TYPES OF OBSERVATIONS

NO. OF DATA RECS IN DATA SET:   23
NO. OF DATA ITEMS IN DATA SET:   4
ID DATA ITEM IS DATA ITEM NO.:   2
DEP VARIABLE IS DATA ITEM NO.:   3

LABELS TO BE USED FOR ITEMS APPEARING
       IN TABLES AND SCATTERPLOTS ARE:
DOSE    TIME    CONC     P/S    PRED    RES     WRES

FORMAT FOR DATA IS:
(4F10.0)

TOT. NO. OF OBS RECS:      23
TOT. NO. OF INDIVIDUALS:   17

LENGTH OF THETA:  3

OMEGA HAS BLOCK FORM:
 1
 1  1

INITIAL ESTIMATE OF THETA:
LOWER BOUND    INITIAL EST    UPPER BOUND
 0.1200e+00     0.6000e+00     0.3000e+01
 0.1000e-01     0.7000e-01     0.4000e+00
 0.6000e+01     0.2810e+02     0.1400e+03

ESTIMATION STEP OMITTED:    NO
NO. OF FUNCT. EVALS. ALLOWED:  450
NO. OF SIG. FIGURES REQUIRED:    4
INTERMEDIATE PRINTOUT:   YES
CONVERGENCE REPEATED:     NO
MSF OUTPUT:               NO

COVARIANCE STEP OMITTED:    NO
EIGENVLS. PRINTED:    NO
SPECIAL COMPUTATION:  NO

TABLES STEP OMITTED:    NO
NO. OF TABLES:       1
TABLES PRINTED:    YES
TABLES FILE USED:   NO

USER CHOSEN DATA ITEMS FOR TABLE  1,
IN THE ORDER THEY WILL APPEAR IN THE TABLE, ARE:
 P/S    TIME
     THE FIRST 2 OF THESE WILL BE SORTED IN THE ORDER IN WHICH THEY APPEAR
```

Fig. 53a

```
SCATTERPLOT STEP OMITTED:    NO
NO. OF PAIRS OF ITEMS GENERATING
        FAMILIES OF SCATTERPLOTS:  9

ITEMS TO BE SCATTERED ARE:    TIME    CONC
ITEMS TO BE SCATTERED ARE:    TIME    CONC
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    TIME    PRED
ITEMS TO BE SCATTERED ARE:    TIME    PRED
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    TIME    RES
ITEMS TO BE SCATTERED ARE:    TIME    RES
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    TIME    WRES
    FOR FIXED VALUES OF ITEMS:     P/S
ITEMS TO BE SCATTERED ARE:    CONC    PRED
    UNIT SLOPE LINE INCLUDED
ITEMS TO BE SCATTERED ARE:    CONC    PRED
    FOR FIXED VALUES OF ITEMS:     P/S
    UNIT SLOPE LINE INCLUDED
```

Fig. 53b

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****
****

FINAL PARAMETER ESTIMATE

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THETA - VECTOR OF FIXED EFFECTS **********

TH 1	TH 2	TH 3
5.65e-01	6.22e-02	2.95e+01

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1	ETA2
ETA1	2.88e-02	
ETA2	-7.55e-04	4.42e-03

Fig. 54

Fig. 55

```
********************************************************************************
********************                                        ********************
********************        STANDARD ERROR OF ESTIMATE      ********************
********************                                        ********************
********************************************************************************
```

THETA - VECTOR OF FIXED EFFECTS *********************

TH 1	TH 2	TH 3
1.21e-02	5.65e-03	1.12e+00

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1	ETA2
ETA1	2.13e-02	
ETA2	7.11e-04	3.34e-03

****
****
****
****

CORRELATION MATRIX OF ESTIMATE

****
****
****
****

	TH 1	TH 2	TH 3	OM11	OM12	OM22
TH 1	1.00e+00					
TH 2	3.76e-01	1.00e+00				
TH 3	-1.13e-01	-9.37e-01	1.00e+00			
OM11	-1.42e-01	-8.94e-01	9.25e-01	1.00e+00		
OM12	-1.54e-01	7.98e-01	-9.03e-01	-9.01e-01	1.00e+00	
OM22	1.07e-01	8.42e-01	-7.70e-01	-7.83e-01	8.00e-01	1.00e+00

Fig. 56

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=SLOPE (LITERS/HR/KG)
C     THETA(2)=INTERCEPT (LITERS/HR)
C     DATREC(2)=WEIGHT (KG)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H
C
      F=THETA(1)*DATREC(2)+THETA(2)
      G(1)=1.
      H(1)=1.
      RETURN
      END
```

```
FILE     NULL
PROB     LIN REGRESSION OF CLEARANCE VS WT; REPEATED MEASURES
DATA        0    0  72    3
ITEM        1    3   0    0    1
LABL       ID       WT       CL
FORM
(F2.0,3X,F4.0,1X,F6.0)
 1    79.6 1.850
 1    79.6 2.642
 1    79.6 1.963
 1    79.6 2.415
 1    79.6 1.905
 1    79.6 2.120
 2    72.4 3.270
 2    72.4 3.600
 2    72.4 3.530
 2    72.4 3.689
 2    72.4 3.940
 2    72.4 4.526
 3    70.5 2.977
 3    70.5 3.143
 3    70.5 3.497
 3    70.5 3.264
 3    70.5 3.447
 3    70.5 3.652
 4    72.7 2.768
 4    72.7 3.183
 4    72.7 3.119
 4    72.7 3.435
 4    72.7 3.520
 4    72.7 3.603
 5    54.6 2.335
 5    54.6 2.241
 5    54.6 2.149
 5    54.6 2.381
 5    54.6 2.184
 5    54.6 1.805
 6    80.0 3.885
 6    80.0 3.079
 6    80.0 3.600
 6    80.0 3.963
 6    80.0 3.598
 6    80.0 3.415
 7    64.6 3.175
 7    64.6 3.260
 7    64.6 3.590
 7    64.6 3.154
 7    64.6 3.616
 7    64.6 3.027
 8    70.5 3.140
 8    70.5 3.310
 8    70.5 3.426
 8    70.5 3.445
 8    70.5 3.237
 8    70.5 3.279
 9    86.4 3.247
 9    86.4 2.628
 9    86.4 3.296
 9    86.4 3.380
 9    86.4 3.621
 9    86.4 3.240
```

```
10    58.2 1.889
10    58.2 2.800
10    58.2 1.865
10    58.2 1.828
10    58.2 3.106
10    58.2 2.386
11    65.0 3.674
11    65.0 4.151
11    65.0 3.670
11    65.0 3.324
11    65.0 4.941
11    65.0 4.129
12    60.5 2.331
12    60.5 2.521
12    60.5 3.194
12    60.5 2.928
12    60.5 2.868
12    60.5 2.406
STRC        2   1   1            1        1
THCN        1
THTA          .04        0
LOWR    -1000000         0
UPPR     1000000         0
DIAG           .4
DIAG           .1
ESTM        0 150   4
COVR        0
TABL        0   1
TABL        2   1        2
SCAT        0   2
SCAT        2   5
SCAT        2   6
```

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                    FINAL PARAMETER ESTIMATE                                              **********
**********                                                                                                          **********
********************************************************************************************************************************

THETA - VECTOR OF FIXED EFFECTS  **********

           TH 1      TH 2

        4.41e-02  0.00e+00


OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  ********

           ETA1

ETA1     3.26e-01


SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS  ****

           EPS1

EPS1     1.25e-01
```

Fig. 59

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                    STANDARD ERROR OF ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************


THETA - VECTOR OF FIXED EFFECTS  **********

           TH 1      TH 2

        2.56e-03 .........


OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  ********

           ETA1

ETA1    1.61e-01


SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS  ****

           EPS1

EPS1    2.65e-02
```

Fig. 60

****
****
****
****

CORRELATION MATRIX OF ESTIMATE

****
****
****
****

	TH 1	TH 2	OM11	SG11
TH 1	1.00e+00			
TH 2	.....	.....		
OM11	-3.75e-01	.....	1.00e+00	
SG11	2.90e-01	.....	2.87e-01	1.00e+00

Fig. 61

Fig. 62

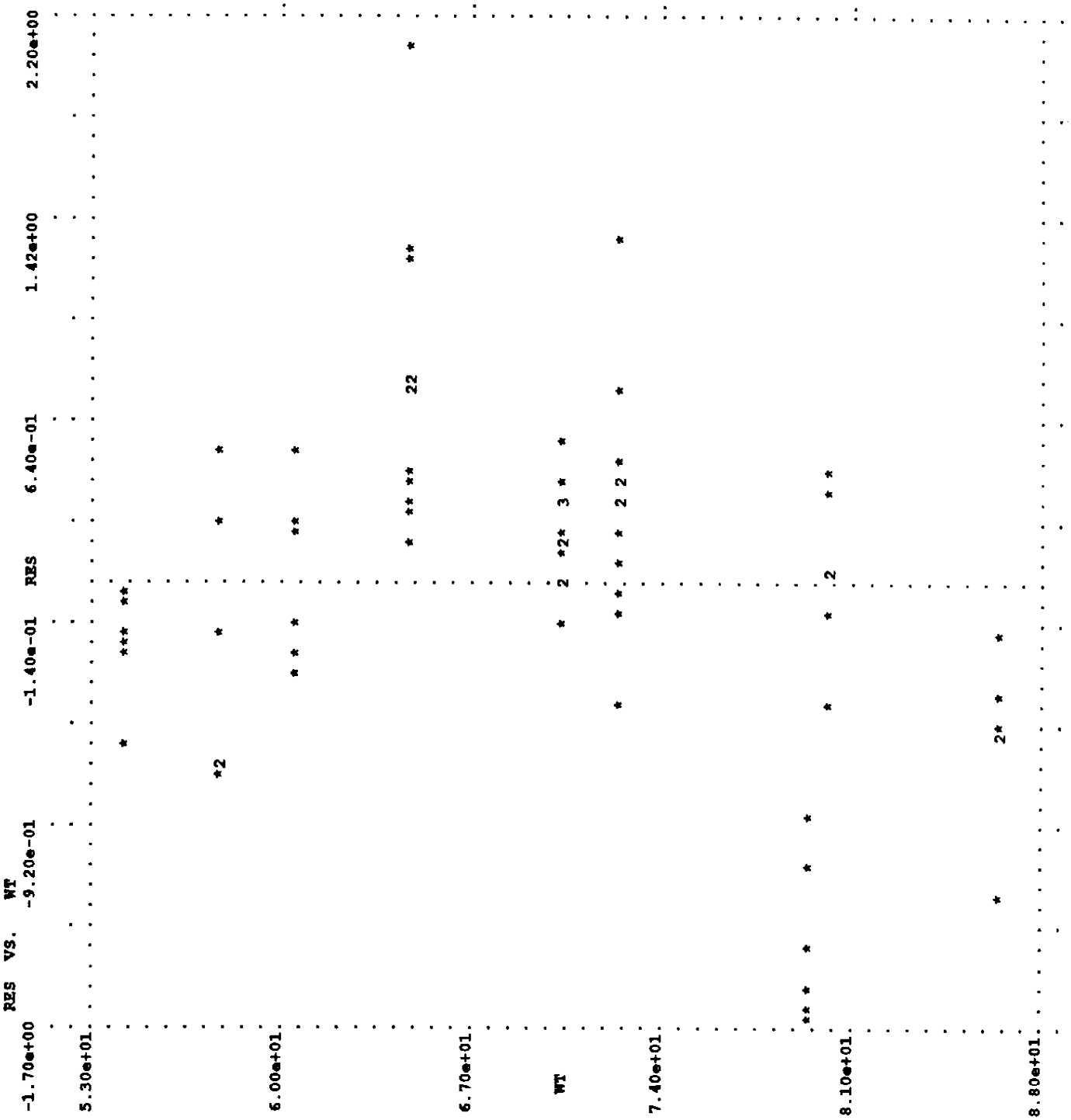
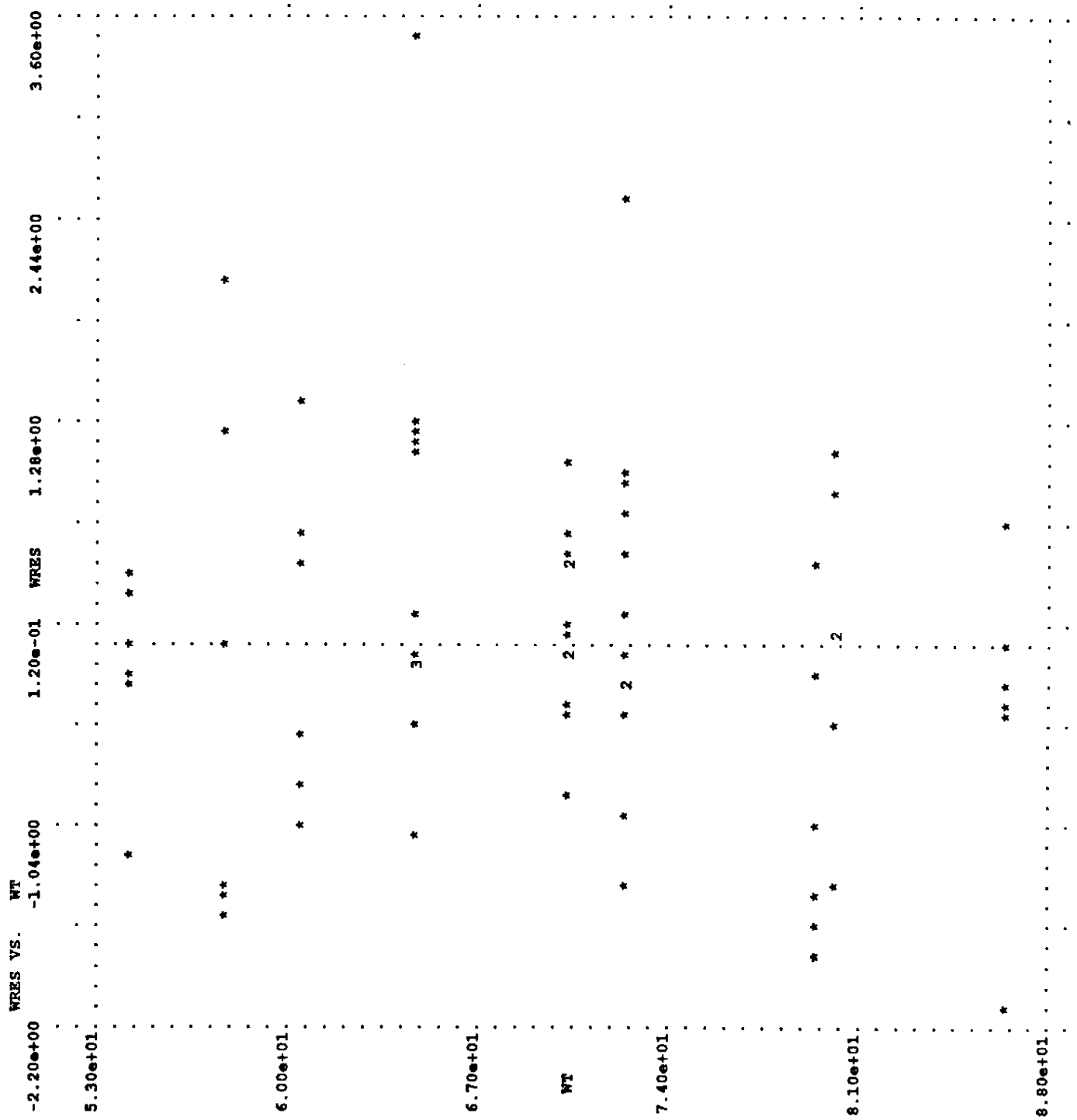

RES VS. WT
-1.70e+00
-9.20e-01
-1.40e-01
1.42e+00
2.20e+00
6.40e-01
RES
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

Fig. 63


WRES VS. WT
-2.20e+00
-1.04e+00
1.20e-01
1.28e+00
2.44e+00
3.60e+00
WRES
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=SLOPE (LITERS/HR/KG)
C     THETA(2)=INTERCEPT (LITERS/HR)
C     THETA(3)=MEAN KE (1/HR)
C     DATREC(2)=WEIGHT (KG)
C     DATREC(4)=TYPE DATA ITEM
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H
C
      IF (DATREC(4).EQ.0.) THEN
         F=THETA(1)*DATREC(2)+THETA(2)
         G(1)=1.
         G(2)=0.
         H(1)=1.
         H(2)=0.
      ELSE
         F=THETA(3)
         G(1)=0.
         G(2)=1.
         H(1)=0.
         H(2)=1.
      ENDIF
      RETURN
      END
```

```
FILE     NULL
PROB     MULTIV LIN REG OF CLEARANCE AND RATE CONSTANT VS WT; REPEATED MEASURES
DATA        0    0 144    5
ITEM        1    3    0    0    1        5
LABL       L1        WT        CL     TYPE       L2
FORM
(F2.0,3X,F4.0,1X,F6.0,2(1X,F1.0))
 1    79.6 1.850
 1    79.6  .0475 1
 1    79.6 2.642    1
 1    79.6  .0558 1 1
 1    79.6 1.963
 1    79.6  .0440 1
 1    79.6 2.415    1
 1    79.6  .0560 1 1
 1    79.6 1.905
 1    79.6  .0442 1
 1    79.6 2.120    1
 1    79.6  .0513 1 1
 2    72.4 3.270
 2    72.4  .0996 1
 2    72.4 3.600    1
 2    72.4  .0919 1 1
 2    72.4 3.530
 2    72.4  .0961 1
 2    72.4 3.689    1
 2    72.4  .0940 1 1
 2    72.4 3.940
 2    72.4  .0996 1
 2    72.4 4.526    1
 2    72.4  .0996 1 1
 3    70.5 2.977
 3    70.5  .0942 1
 3    70.5 3.143    1
 3    70.5  .0731 1 1
 3    70.5 3.497
 3    70.5  .1000 1
 3    70.5 3.264    1
 3    70.5  .0843 1 1
 3    70.5 3.447
 3    70.5  .0818 1
 3    70.5 3.652    1
 3    70.5  .0986 1 1
 4    72.7 2.768
 4    72.7  .0922 1
 4    72.7 3.183    1
 4    72.7  .0885 1 1
 4    72.7 3.119
 4    72.7  .0859 1
 4    72.7 3.435    1
 4    72.7  .0926 1 1
 4    72.7 3.520
 4    72.7  .0968 1
 4    72.7 3.603    1
 4    72.7  .0880 1 1
```

```
5    54.6 2.335
5    54.6  .0840 1
5    54.6 2.241    1
5    54.6  .0907 1 1
5    54.6 2.149
5    54.6  .0910 1
5    54.6 2.381    1
5    54.6  .0866 1 1
5    54.6 2.184
5    54.6  .0842 1
5    54.6 1.805    1
5    54.6  .0651 1 1
6    80.0 3.885
6    80.0  .0881 1
6    80.0 3.079    1
6    80.0  .0758 1 1
6    80.0 3.600
6    80.0  .0739 1
6    80.0 3.963    1
6    80.0  .0982 1 1
6    80.0 3.598
6    80.0  .0751 1
6    80.0 3.415    1
6    80.0  .0947 1 1
7    64.6 3.175
7    64.6  .0897 1
7    64.6 3.260    1
7    64.6  .0997 1 1
7    64.6 3.590
7    64.6  .1033 1
7    64.6 3.154    1
7    64.6  .0890 1 1
7    64.6 3.616
7    64.6  .0951 1
7    64.6 3.027    1
7    64.6  .0871 1 1
8    70.5 3.140
8    70.5  .0814 1
8    70.5 3.310    1
8    70.5  .0859 1 1
8    70.5 3.426
8    70.5  .0875 1
8    70.5 3.445    1
8    70.5  .0732 1 1
8    70.5 3.237
8    70.5  .0767 1
8    70.5 3.279    1
8    70.5  .0834 1 1
9    86.4 3.247
9    86.4  .0784 1
9    86.4 2.628    1
9    86.4  .0550 1 1
9    86.4 3.296
9    86.4  .0878 1
9    86.4 3.380    1
9    86.4  .0663 1 1
9    86.4 3.621
9    86.4  .0761 1
9    86.4 3.240    1
9    86.4  .0741 1 1
```

```
10    58.2 1.889
10    58.2  .0722 1
10    58.2 2.800    1
10    58.2  .0900 1 1
10    58.2 1.865
10    58.2  .0578 1
10    58.2 1.828    1
10    58.2  .0575 1 1
10    58.2 3.106
10    58.2  .0957 1
10    58.2 2.386    1
10    58.2  .0730 1 1
11    65.0 3.674
11    65.0  .0945 1
11    65.0 4.151    1
11    65.0  .1026 1 1
11    65.0 3.670
11    65.0  .1092 1
11    65.0 3.324    1
11    65.0  .0911 1 1
11    65.0 4.941
11    65.0  .0939 1
11    65.0 4.129    1
11    65.0  .0947 1 1
12    60.5 2.331
12    60.5  .1039 1
12    60.5 2.521    1
12    60.5  .0807 1 1
12    60.5 3.194
12    60.5  .1006 1
12    60.5 2.928    1
12    60.5  .1131 1 1
12    60.5 2.868
12    60.5  .1000 1
12    60.5 2.406    1
12    60.5  .0730 1 1
STRC        3   2   2                1       1
STRC        1   2
STRC        1   2
THCN        1
THTA          .04       0     .08
LOWR    -1000000       0-1000000
UPPR     1000000       0 1000000
BLST          .4    .006   .0002
BLST          .1    .002  .00008
ESTM        0 500   4   5
COVR        0
TABL        0   1
TABL        3   1   2   2   0   4   1
SCAT        0   2
SCAT        2   7   1   4
SCAT        2   8   1   4
```

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                      FINAL PARAMETER ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************
```

THETA - VECTOR OF FIXED EFFECTS **********

TH 1	TH 2	TH 3
4.46e-02	0.00e+00	8.43e-02

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1	ETA2
ETA1	3.27e-01	
ETA2	6.72e-03	1.54e-04

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

	EPS1	EPS2
EPS1	1.25e-01	
EPS2	1.73e-03	9.21e-05

Fig. 66

```
********************************************************************************************************************************
**********                                                                                                          **********
**********                                    STANDARD ERROR OF ESTIMATE                                            **********
**********                                                                                                          **********
********************************************************************************************************************************


THETA - VECTOR OF FIXED EFFECTS  **********

           TH 1      TH 2      TH 3

        2.30e-03 .........  3.68e-03


OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  ********

           ETA1      ETA2

ETA1    1.62e-01

ETA2    3.71e-03  9.05e-05


SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS  ****

           EPS1      EPS2

EPS1    2.65e-02

EPS2    6.18e-04  2.23e-05
```

Fig. 67

Fig. 68

CORRELATION MATRIX OF ESTIMATE

	TH 1	TH 2	TH 3	OM11	OM12	OM22	SG11	SG12	SG22
TH 1	1.00e+00								
TH 2	....	....							
TH 3	9.08e-01	....	1.00e+00						
OM11	-3.16e-01	....	-5.17e-01	1.00e+00					
OM12	-5.05e-01	....	-6.43e-01	9.61e-01	1.00e+00				
OM22	-6.10e-01	....	-6.87e-01	8.86e-01	9.77e-01	1.00e+00			
SG11	2.22e-01	....	3.92e-02	2.78e-01	1.42e-01	4.07e-02	1.00e+00		
SG12	-4.02e-01	....	-3.50e-01	-2.14e-01	-1.25e-01	-5.05e-02	4.03e-01	1.00e+00	
SG22	-1.67e-01	....	-3.13e-02	-3.71e-01	-3.39e-01	-2.71e-01	2.83e-01	8.25e-01	1.00e+00

TABLE NO. 1

LINE NO.	TYPE	L1	WT	CL	PRED	RES	WRES
1	0.00e+00	1.00e+00	7.96e+01	1.85e+00	3.55e+00	-1.70e+00	-1.80e+00
2	0.00e+00	1.00e+00	7.96e+01	2.41e+00	3.55e+00	-1.13e+00	-2.11e-01
3	0.00e+00	1.00e+00	7.96e+01	2.64e+00	3.55e+00	-9.05e-01	4.35e-01
4	0.00e+00	1.00e+00	7.96e+01	1.96e+00	3.55e+00	-1.58e+00	-1.48e+00
5	0.00e+00	1.00e+00	7.96e+01	2.12e+00	3.55e+00	-1.43e+00	-1.04e+00
6	0.00e+00	1.00e+00	7.96e+01	1.90e+00	3.55e+00	-1.64e+00	-1.64e+00
7	0.00e+00	2.00e+00	7.24e+01	3.27e+00	3.23e+00	4.35e-02	-1.03e+00
8	0.00e+00	2.00e+00	7.24e+01	3.94e+00	3.23e+00	7.13e-01	8.76e-01
9	0.00e+00	2.00e+00	7.24e+01	3.69e+00	3.23e+00	4.62e-01	1.70e-01
10	0.00e+00	2.00e+00	7.24e+01	3.60e+00	3.23e+00	3.73e-01	-7.94e-02
11	0.00e+00	2.00e+00	7.24e+01	3.53e+00	3.23e+00	3.03e-01	-2.85e-01
12	0.00e+00	2.00e+00	7.24e+01	4.53e+00	3.23e+00	1.30e+00	2.54e+00
13	0.00e+00	3.00e+00	7.05e+01	2.98e+00	3.14e+00	-1.65e-01	-8.84e-01
14	0.00e+00	3.00e+00	7.05e+01	3.14e+00	3.14e+00	1.14e-03	-3.77e-01
15	0.00e+00	3.00e+00	7.05e+01	3.45e+00	3.14e+00	3.05e-01	4.73e-01
16	0.00e+00	3.00e+00	7.05e+01	3.65e+00	3.14e+00	5.10e-01	1.03e+00
17	0.00e+00	3.00e+00	7.05e+01	3.26e+00	3.14e+00	1.22e-01	-5.15e-02
18	0.00e+00	3.00e+00	7.05e+01	3.50e+00	3.14e+00	3.55e-01	5.86e-01
19	0.00e+00	4.00e+00	7.27e+01	3.52e+00	3.24e+00	2.80e-01	7.10e-01
20	0.00e+00	4.00e+00	7.27e+01	3.18e+00	3.24e+00	-5.69e-02	-2.35e-01
21	0.00e+00	4.00e+00	7.27e+01	3.60e+00	3.24e+00	3.63e-01	9.61e-01
22	0.00e+00	4.00e+00	7.27e+01	3.43e+00	3.24e+00	1.95e-01	4.75e-01
23	0.00e+00	4.00e+00	7.27e+01	2.77e+00	3.24e+00	-4.72e-01	-1.42e+00
24	0.00e+00	4.00e+00	7.27e+01	3.12e+00	3.24e+00	-1.21e-01	-4.13e-01
25	0.00e+00	5.00e+00	5.46e+01	2.18e+00	2.43e+00	-2.49e-01	-1.77e-01

Fig. 69a

LINE NO.	TYPE	L1	WT	CL	PRED	RES	WRES
130	1.00e+00	1.00e+01	5.82e+01	5.78e-02	8.43e-02	-2.65e-02	-1.60e+00
131	1.00e+00	1.00e+01	5.82e+01	9.00e-02	8.43e-02	5.75e-03	7.69e-01
132	1.00e+00	1.00e+01	5.82e+01	7.22e-02	8.43e-02	-1.21e-02	1.03e-01
133	1.00e+00	1.10e+01	6.50e+01	9.45e-02	8.43e-02	1.02e-02	-5.09e-01
134	1.00e+00	1.10e+01	6.50e+01	9.47e-02	8.43e-02	1.04e-02	-1.23e+00
135	1.00e+00	1.10e+01	6.50e+01	1.03e-01	8.43e-02	1.83e-02	-3.09e-01
136	1.00e+00	1.10e+01	6.50e+01	9.39e-02	8.43e-02	9.65e-03	-2.66e+00
137	1.00e+00	1.10e+01	6.50e+01	1.09e-01	8.43e-02	2.49e-02	1.28e+00
138	1.00e+00	1.10e+01	6.50e+01	9.11e-02	8.43e-02	6.85e-03	-3.48e-01
139	1.00e+00	1.20e+01	6.05e+01	1.13e-01	8.43e-02	2.88e-02	2.63e+00
140	1.00e+00	1.20e+01	6.05e+01	1.00e-01	8.43e-02	1.57e-02	1.14e+00
141	1.00e+00	1.20e+01	6.05e+01	8.07e-02	8.43e-02	-3.55e-03	-6.32e-01
142	1.00e+00	1.20e+01	6.05e+01	1.01e-01	8.43e-02	1.63e-02	6.78e-01
143	1.00e+00	1.20e+01	6.05e+01	1.04e-01	8.43e-02	1.96e-02	2.49e+00
144	1.00e+00	1.20e+01	6.05e+01	7.30e-02	8.43e-02	-1.13e-02	-1.38e+00

Fig. 69b

Fig. 70

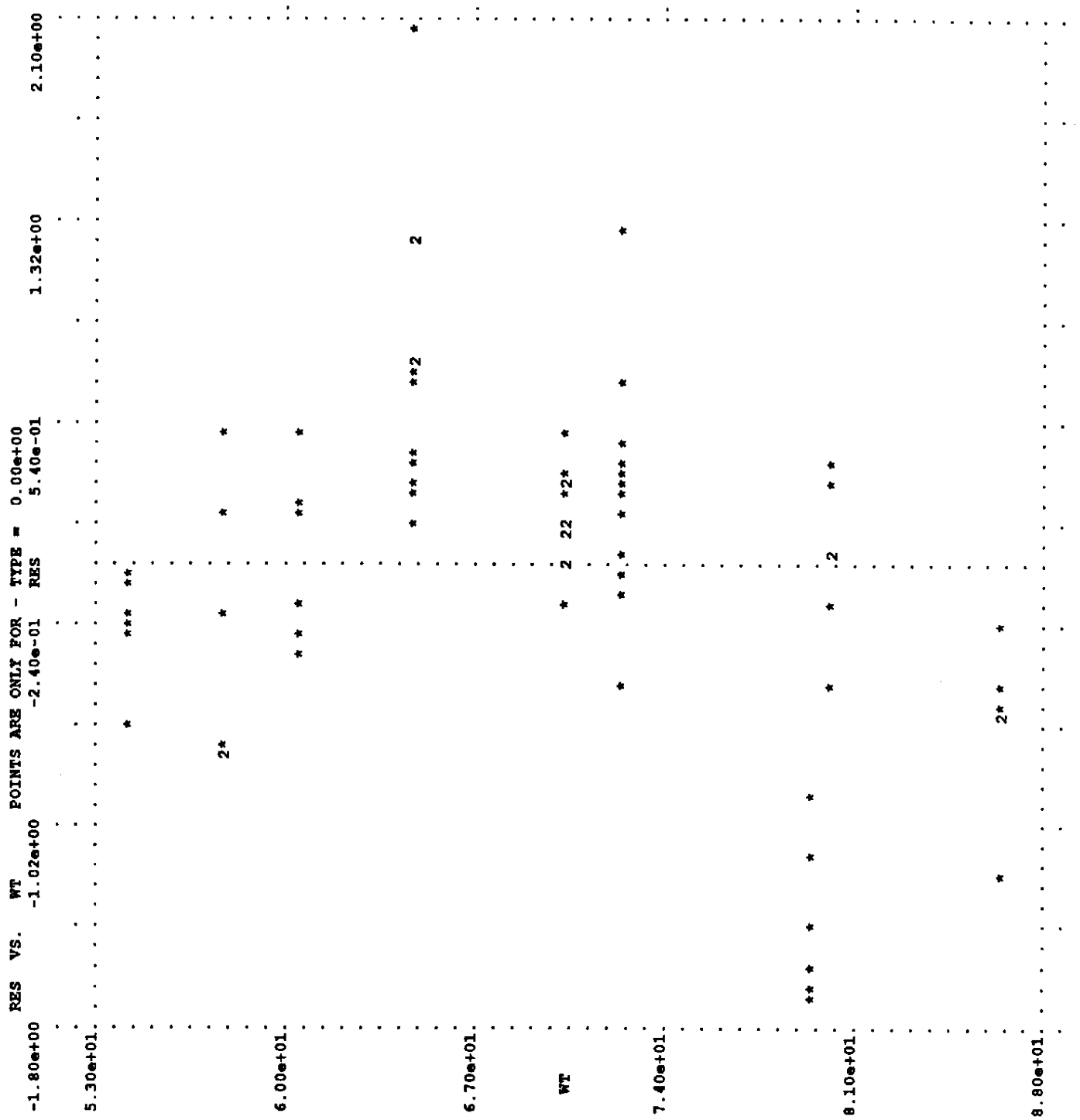

RES VS. WT POINTS ARE ONLY FOR - TYPE = 0.00e+00
-1.80e+00
-1.02e+00
-2.40e-01
1.32e+00
2.10e+00
RES
5.40e-01
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

Fig. 71

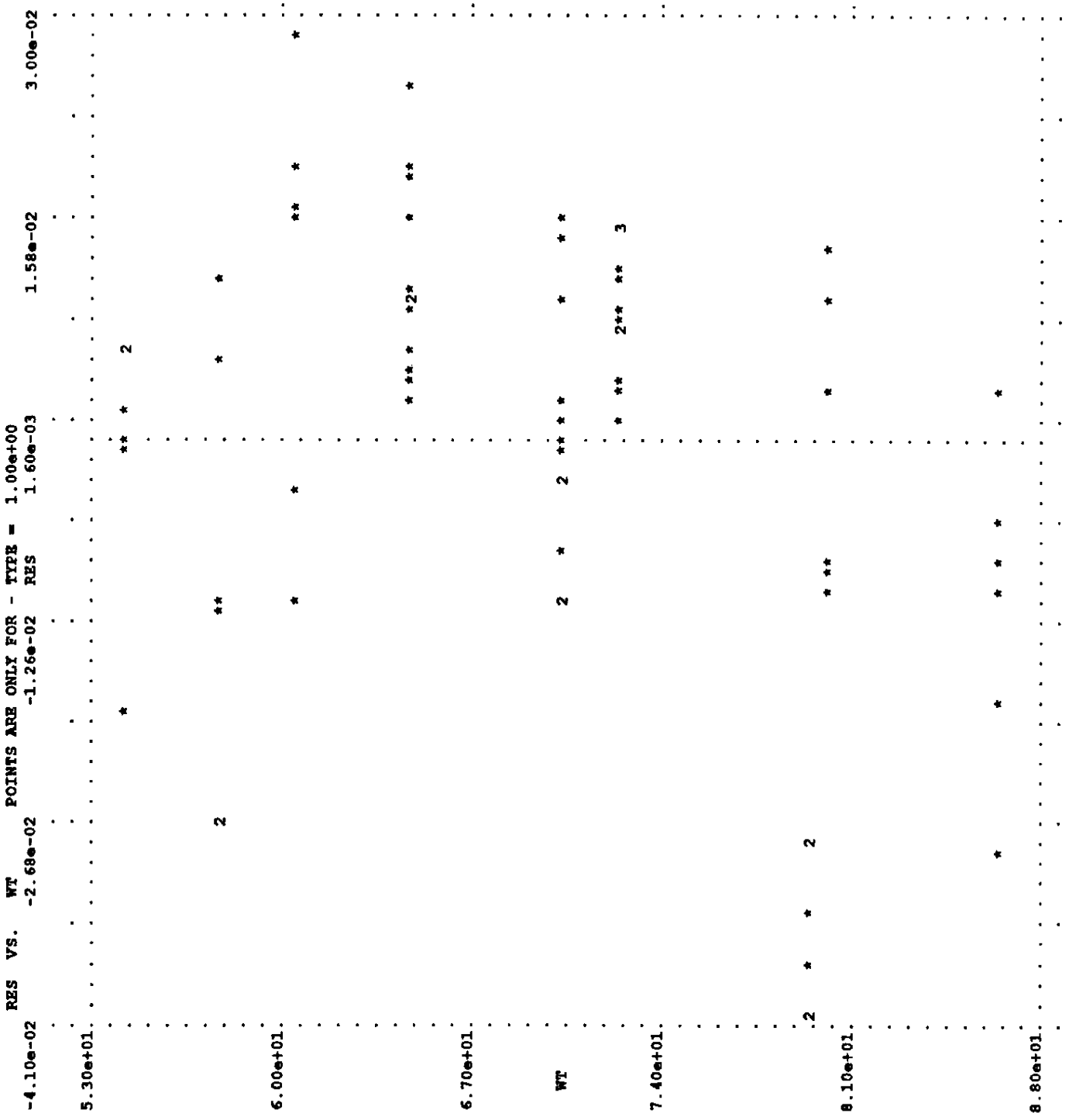

RES VS. WT POINTS ARE ONLY FOR - TYPE = 1.00e+00
-4.10e-02
-2.68e-02
-1.26e-02
1.60e-03
1.58e-02
3.00e-02
RES
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT

Fig. 72

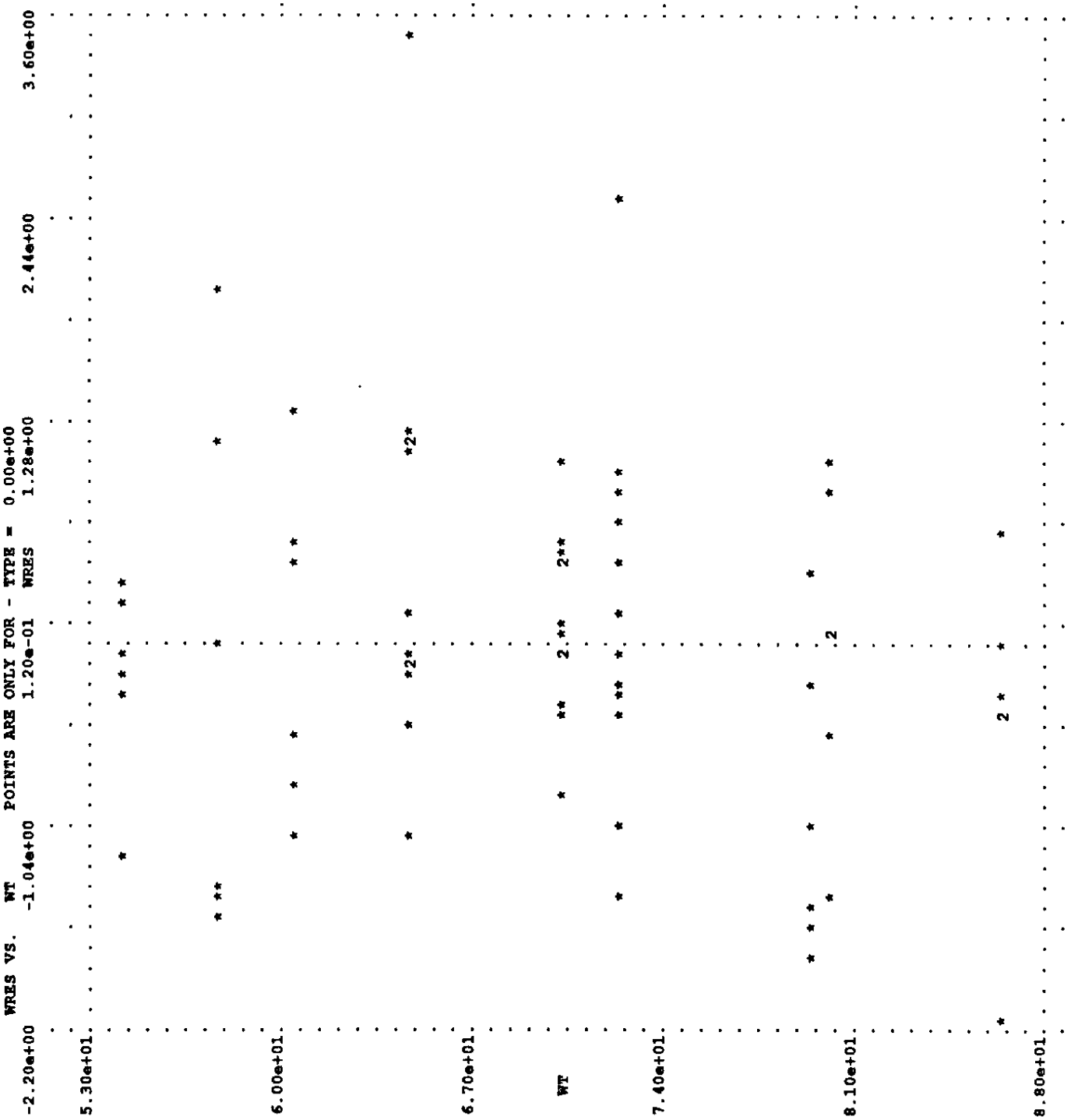
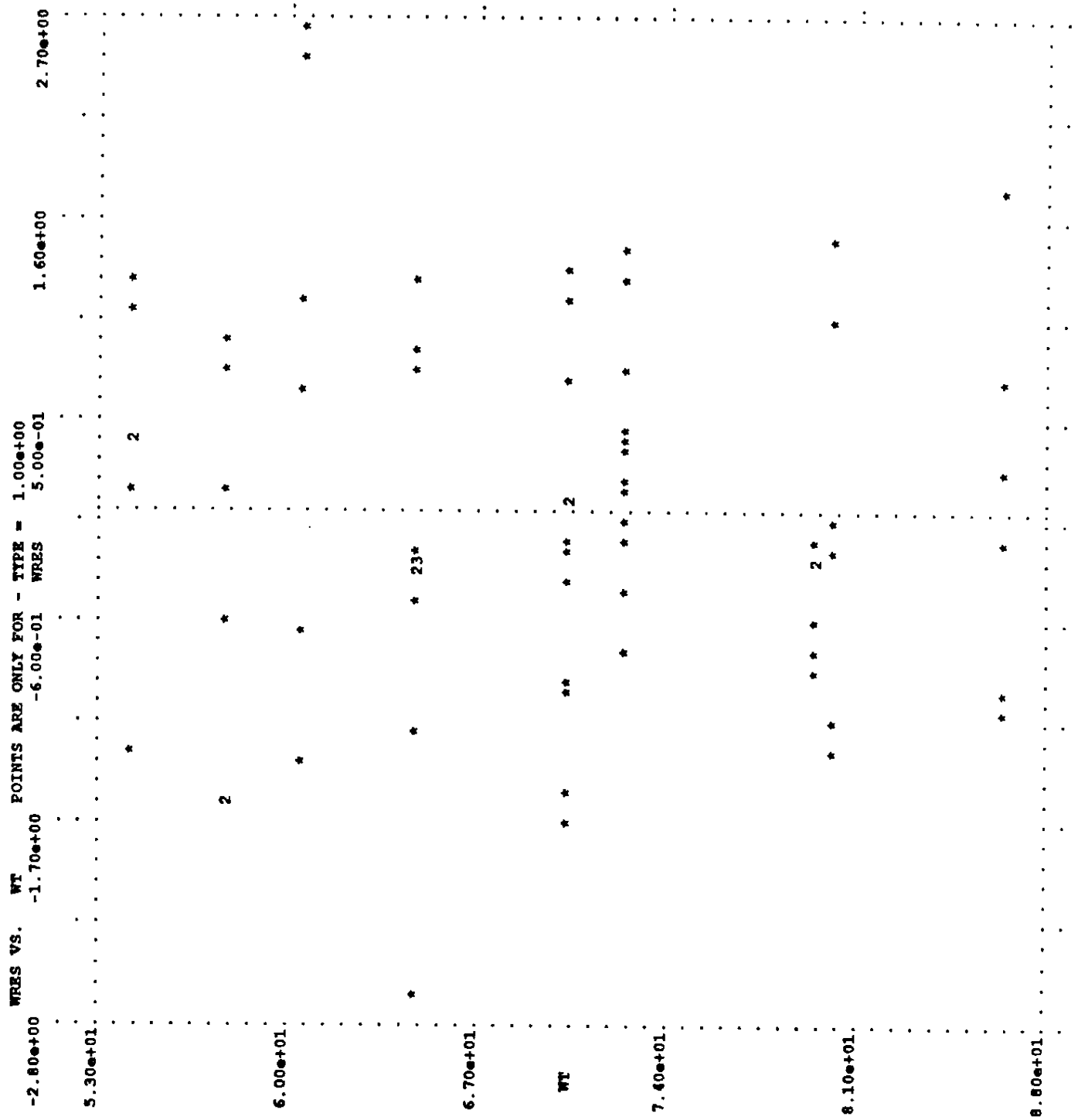

WRES VS. WT POINTS ARE ONLY FOR - TYPE = 0.00e+00
-2.20e+00
-1.04e+00
1.20e-01
1.28e+00
2.44e+00
3.60e+00
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT
WRES

Fig. 73


WRES VS. WT POINTS ARE ONLY FOR - TYPE = 1.00e+00
-2.80e+00
-1.70e+00
-6.00e-01
5.00e-01
1.60e+00
2.70e+00
5.30e+01
6.00e+01
6.70e+01
7.40e+01
8.10e+01
8.80e+01
WT
WRES

```
      SUBROUTINE PRED (ICALL,NEWIND,THETA,DATREC,INDXS,F,G,H)
C
C     THETA(1)=MEAN ABSORPTION RATE CONSTANT (1/HR)
C     THETA(2)=MEAN ELIMINATION RATE CONSTANT (1/HR)
C     THETA(3)=SLOPE OF CLEARANCE VS WEIGHT RELATIONSHIP (LITERS/HR/KG)
C     DATREC(2)=WEIGHT-ADJUSTED DOSE (MG/KG)
C     DATREC(3)=TIME (HR)
C     DATREC(5)=WEIGHT (KG)
C
      DIMENSION THETA(*),DATREC(*),INDXS(*),G(*),H(*)
      DOUBLE PRECISION THETA,F,G,H,A,B,C,D,E
      DOUBLE PRECISION DAD2,DBD1,DFD1,DFD2,DFDD,DFDE
C
      IF (NEWIND.NE.2) THEN
         DOSE=DATREC(2)
         WT=DATREC(5)
      ENDIF
      A=EXP(-THETA(2)*DATREC(3))
              DAD2=-DATREC(3)*A
      B=EXP(-THETA(1)*DATREC(3))
              DBD1=-DATREC(3)*B
      C=THETA(1)-THETA(2)
      D=A-B
      E=THETA(3)*C
      F=((DOSE*THETA(1)*THETA(2))/E)*D
              DFD1=((DOSE*THETA(2))/E)*D
              DFD2=((DOSE*THETA(1))/E)*D
              DFDD=(DOSE*THETA(1)*THETA(2))/E
              DFDE=-((DOSE*THETA(1)*THETA(2))/E**2)*D
      G(1)=DFD1-DFDD*DBD1+DFDE*THETA(3)
      G(2)=DFD2+DFDD*DAD2-DFDE*THETA(3)
      G(3)=DFDE*C/WT
      H(1)=1.
      RETURN
      END
```

```
FILE    NULL
PROB    NONLINEAR REGRESSION OF CP VS TIME DATA FROM 12 SUBJECTS
DATA       0    0 132    5
ITEM       1    4    0    0    1
LABL    ID       DOSE     TIME     CP       WT
FORM
(5F10.0)
          1       4.02       0.        .74      79.6
          1                  0.25     2.84
          1                  0.57     6.57
          1                  1.12    10.5
          1                  2.02     9.66
          1                  3.82     8.58
          1                  5.1      8.36
          1                  9.05     6.89
          1                  7.03     7.47
          1                 12.12     5.94
          1                 24.37     3.28
          2       4.4        0.       0.       72.4
          2                   .27     1.72
          2                   .52     7.91
          2                  1.       8.31
          2                  1.92     8.33
          2                  3.5      6.85
          2                  5.02     6.08
          2                  7.03     5.4
          2                  9.       4.55
          2                 12.       3.01
          2                 24.3       .90
          3       4.53       0.       0.       70.5
          3                   .27     4.4
          3                   .58     6.9
          3                  1.02     8.2
          3                  2.02     7.8
          3                  3.62     7.5
          3                  5.08     6.2
          3                  7.07     5.3
          3                  9.       4.9
          3                 12.15     3.7
          3                 24.17     1.05
          4       4.4        0.       0.       72.7
          4                   .35     1.89
          4                   .6      4.6
          4                  1.07     8.6
          4                  2.13     8.38
          4                  3.5      7.54
          4                  5.02     6.88
          4                  7.02     5.78
          4                  9.02     5.33
          4                 11.98     4.19
          4                 24.65     1.15
          5       5.86       0.       0.       54.6
          5                   .3      2.02
          5                   .52     5.63
          5                  1.       11.4
          5                  2.02     9.33
          5                  3.5      8.74
          5                  5.02     7.56
          5                  7.02     7.09
          5                  9.1      5.9
          5                 12.       4.37
          5                 24.35     1.57
```

6	4.	0.	0.	80.
6		.27	1.29	
6		.58	3.08	
6		1.15	6.44	
6		2.03	6.32	
6		3.57	5.53	
6		5.	4.94	
6		7.	4.02	
6		9.22	3.46	
6		12.1	2.78	
6		23.85	.92	
7	4.95	0.	.15	64.6
7		.25	.85	
7		.5	2.35	
7		1.02	5.02	
7		2.02	6.58	
7		3.48	7.09	
7		5.	6.66	
7		6.98	5.25	
7		9.	4.39	
7		12.05	3.53	
7		24.22	1.15	
8	4.53	0.	0.	70.5
8		.25	3.05	
8		0.52	3.05	
8		.98	7.31	
8		2.02	7.56	
8		3.53	6.59	
8		5.05	5.88	
8		7.15	4.73	
8		9.07	4.57	
8		12.1	3.	
8		24.12	1.25	
9	3.1	.0	.0	86.4
9		.3	7.37	
9		.63	9.03	
9		1.05	7.14	
9		2.02	6.33	
9		3.53	5.66	
9		5.02	5.67	
9		7.17	4.24	
9		8.8	4.11	
9		11.6	3.16	
9		24.43	1.12	
10	5.5	0.	.24	58.2
10		.37	2.89	
10		.77	5.22	
10		1.02	6.41	
10		2.05	7.83	
10		3.55	10.21	
10		5.05	9.18	
10		7.08	8.02	
10		9.38	7.14	
10		12.1	5.68	
10		23.7	2.42	

```
11       4.92        0.          0.        65.
11                    .25        4.86
11                     .5        7.24
11                     .98       8.
11                    1.98       6.81
11                    3.6        5.87
11                    5.02       5.22
11                    7.03       4.45
11                    9.03       3.62
11                   12.12       2.69
11                   24.08        .86
12       5.3         0.          0.        60.5
12                    .25        1.25
12                     .5        3.96
12                    1.         7.82
12                    2.         9.72
12                    3.52       9.75
12                    5.07       8.57
12                    7.07       6.59
12                    9.03       6.11
12                   12.05       4.57
12                   24.15       1.17
STRC      3   3   1                  1   1
STRC      1   3
THCN      1
THTA          3.      .08      .04
LOWR          .1     .008     .004
UPPR          5.       .5       .9
BLST          6.     .005       .3   .0002     .006       .4
DIAG        .4
ESTM      0 450   3   5
COVR      0
TABL      0   1
TABL      4   1       2        5        3
SCAT      0   2
SCAT      3   7   1   1
SCAT      3   8   1   1
```

****
****
****
****
****

FINAL PARAMETER ESTIMATE

****
****
****
****
****

THETA - VECTOR OF FIXED EFFECTS **********

TH 1	TH 2	TH 3
2.77e+00	7.81e-02	3.63e-02

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1	ETA2	ETA3
ETA1	5.55e+00		
ETA2	5.24e-03	2.40e-04	
ETA3	-1.28e-01	9.11e-03	5.15e-01

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

	EPS1
EPS1	3.88e-01

Fig. 76

****
****
****
****
****

STANDARD ERROR OF ESTIMATE

THETA - VECTOR OF FIXED EFFECTS **********

TH 1	TH 2	TH 3
7.01e-01	7.36e-03	4.66e-03

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1	ETA2	ETA3
ETA1	4.78e+00		
ETA2	1.24e-02	1.18e-04	
ETA3	4.25e-01	3.62e-03	2.08e-01

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

	EPS1
EPS1	1.06e-01

****
****
****
****

CORRELATION MATRIX OF ESTIMATE

****
****
****
****

	TH 1	TH 2	TH 3	OM11	OM12	OM13	OM22	OM23	OM33	SG11
TH 1	1.00e+00									
TH 2	1.83e-01	1.00e+00								
TH 3	-1.61e-02	9.52e-01	1.00e+00							
OM11	9.70e-01	1.48e-01	-3.71e-02	1.00e+00						
OM12	3.80e-01	7.48e-01	6.54e-01	2.82e-01	1.00e+00					
OM13	-9.82e-02	4.62e-01	5.17e-01	-2.30e-01	6.93e-01	1.00e+00				
OM22	3.43e-02	4.55e-01	3.90e-01	-4.95e-02	7.99e-01	6.61e-01	1.00e+00			
OM23	-3.25e-02	-9.02e-02	-5.88e-02	-1.64e-01	3.57e-01	6.19e-01	6.69e-01	1.00e+00		
OM33	1.56e-02	-2.64e-01	-1.75e-01	-1.08e-01	1.13e-01	4.75e-01	3.04e-01	8.93e-01	1.00e+00	
SG11	-1.70e-01	2.57e-01	1.32e-01	-2.64e-01	4.84e-01	3.66e-01	6.11e-01	2.65e-01	-4.85e-02	1.00e+00

Fig. 78

TABLE NO. 1

LINE NO.	ID	DOSE	WT	TIME	CP	PRED	RES	WRES
1	1.00e+00	4.02e+00	7.96e+01	0.00e+00	7.40e-01	0.00e+00	7.40e-01	1.19e+00
2	1.00e+00	0.00e+00	0.00e+00	2.50e-01	2.84e+00	4.28e+00	-1.44e+00	-1.35e+00
3	1.00e+00	0.00e+00	0.00e+00	5.70e-01	6.57e+00	6.68e+00	-1.12e-01	-2.59e-01
4	1.00e+00	0.00e+00	0.00e+00	1.12e+00	1.05e+01	7.76e+00	2.74e+00	2.50e+00
5	1.00e+00	0.00e+00	0.00e+00	2.02e+00	9.66e+00	7.57e+00	2.09e+00	4.50e-01
6	1.00e+00	0.00e+00	0.00e+00	3.82e+00	8.58e+00	6.60e+00	1.98e+00	9.26e-02
7	1.00e+00	0.00e+00	0.00e+00	5.10e+00	8.36e+00	5.98e+00	2.38e+00	7.70e-01
8	1.00e+00	0.00e+00	0.00e+00	9.05e+00	6.89e+00	4.39e+00	2.50e+00	1.16e+00
9	1.00e+00	0.00e+00	0.00e+00	7.03e+00	7.47e+00	5.14e+00	2.33e+00	7.63e-01
10	1.00e+00	0.00e+00	0.00e+00	1.21e+01	5.94e+00	3.45e+00	2.49e+00	1.37e+00
11	1.00e+00	0.00e+00	0.00e+00	2.44e+01	3.28e+00	1.33e+00	1.95e+00	1.56e+00
12	2.00e+00	4.40e+00	7.24e+01	0.00e+00	0.00e+00	0.00e+00	0.00e+00	0.00e+00
13	2.00e+00	0.00e+00	0.00e+00	2.70e-01	1.72e+00	4.93e+00	-3.21e+00	-3.63e+00
14	2.00e+00	0.00e+00	0.00e+00	5.20e-01	7.91e+00	7.05e+00	8.58e-01	2.85e+00
15	2.00e+00	0.00e+00	0.00e+00	1.00e+00	8.31e+00	8.40e+00	-9.23e-02	6.28e-01
16	2.00e+00	0.00e+00	0.00e+00	1.92e+00	8.33e+00	8.34e+00	-8.12e-03	2.06e-01
17	2.00e+00	0.00e+00	0.00e+00	3.50e+00	6.85e+00	7.41e+00	-5.61e-01	-6.63e-01
18	2.00e+00	0.00e+00	0.00e+00	5.02e+00	6.08e+00	6.58e+00	-5.02e-01	-4.75e-01
19	2.00e+00	0.00e+00	0.00e+00	7.03e+00	5.40e+00	5.63e+00	-2.25e-01	5.94e-02
20	2.00e+00	0.00e+00	0.00e+00	9.00e+00	4.55e+00	4.82e+00	-2.73e-01	3.90e-02
21	2.00e+00	0.00e+00	0.00e+00	1.20e+01	3.01e+00	3.82e+00	-8.05e-01	-7.76e-01
22	2.00e+00	0.00e+00	0.00e+00	2.43e+01	9.00e-01	1.46e+00	-5.59e-01	-4.81e-01
23	3.00e+00	4.53e+00	7.05e+01	0.00e+00	0.00e+00	0.00e+00	0.00e+00	0.00e+00
24	3.00e+00	0.00e+00	0.00e+00	2.70e-01	4.40e+00	5.08e+00	-6.78e-01	-1.80e-01
25	3.00e+00	0.00e+00	0.00e+00	5.80e-01	6.90e+00	7.58e+00	-6.79e-01	-8.43e-02

Fig. 79

Fig. 80

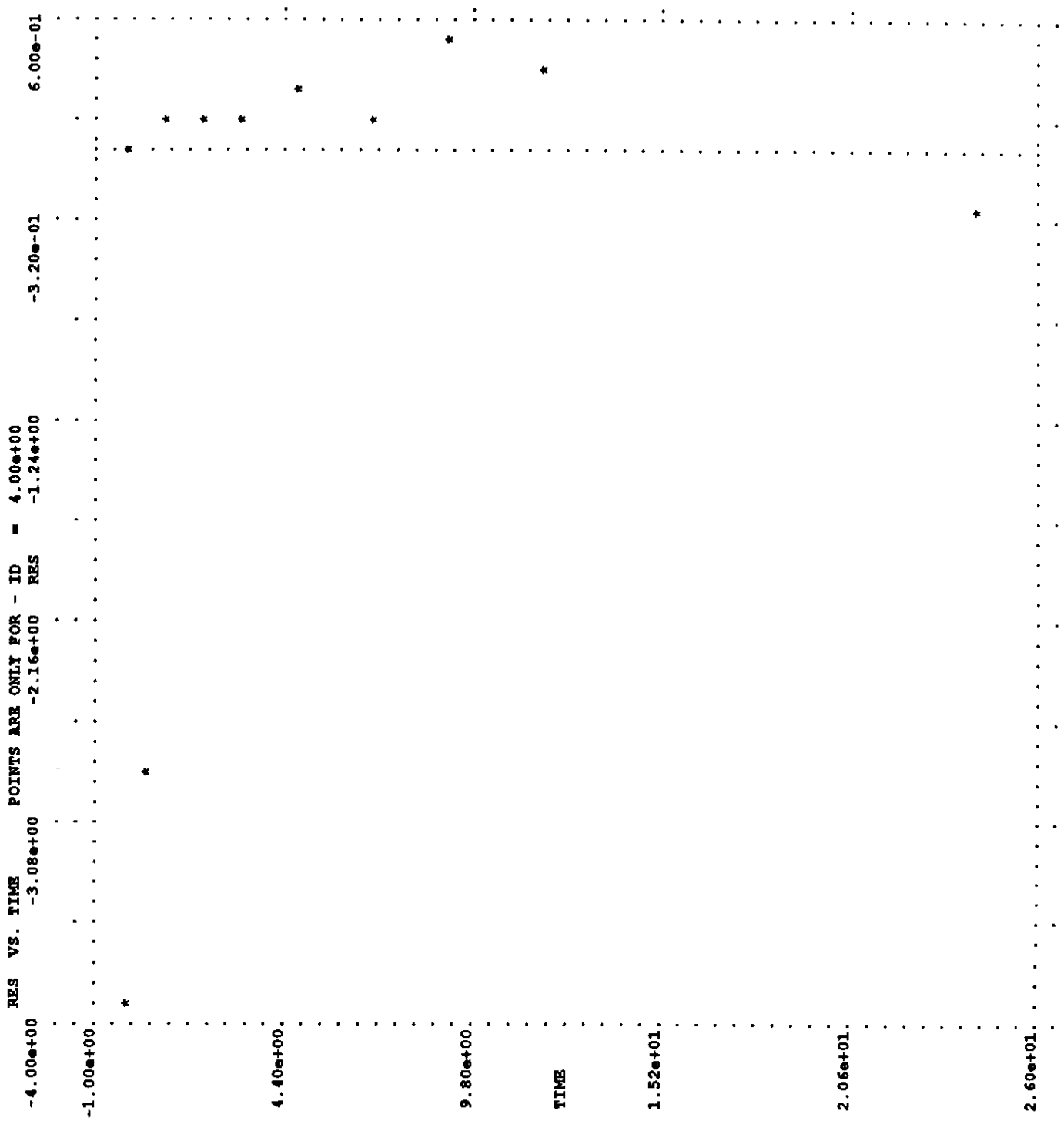

RES VS. TIME POINTS ARE ONLY FOR - ID = 4.00e+00
-4.00e+00
-3.08e+00
-2.16e+00
RES
-1.24e+00
-3.20e-01
6.00e-01
-1.00e+00
4.40e+00
9.80e+00
TIME
1.52e+01
2.06e+01
2.60e+01

Fig. 81

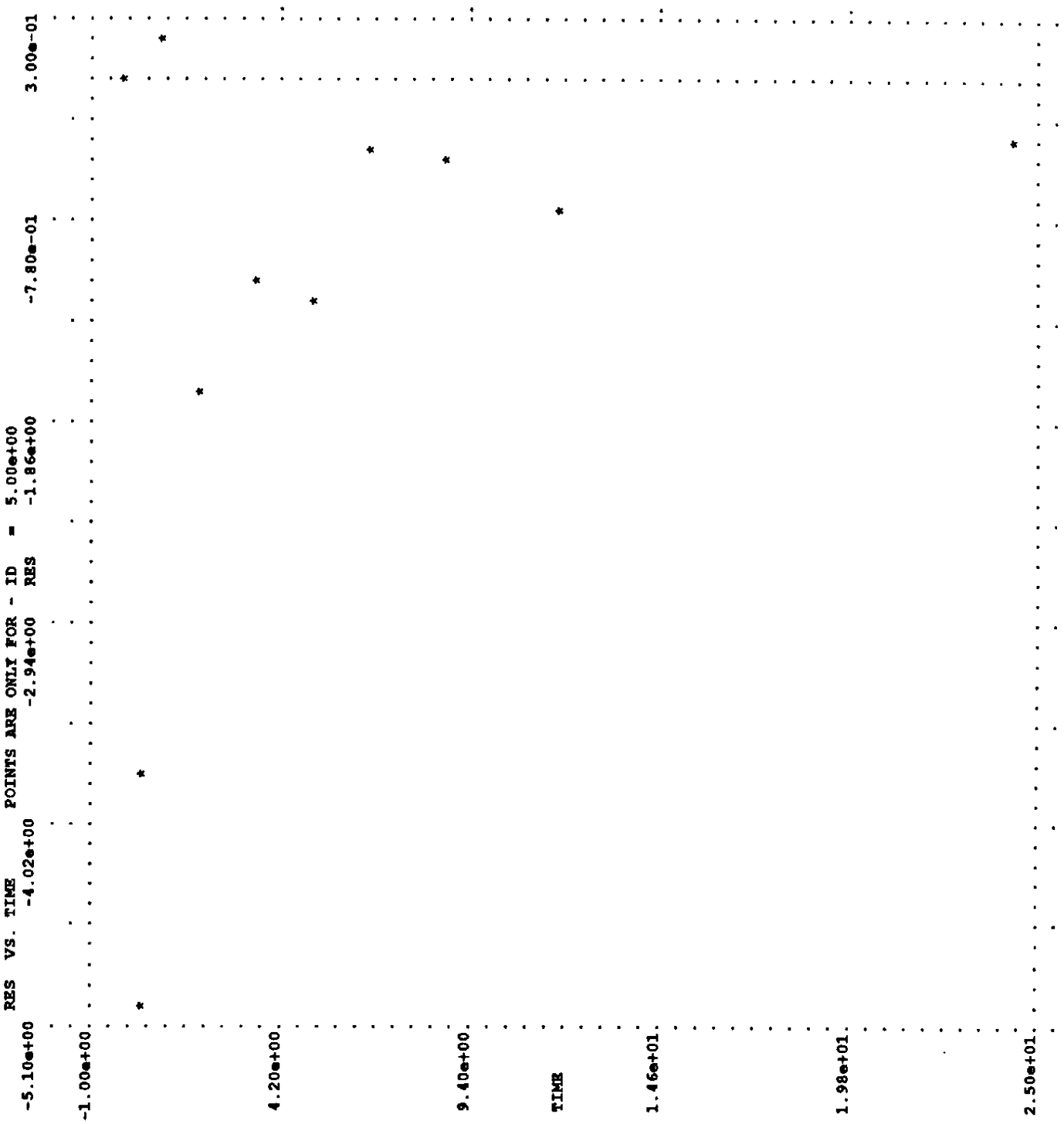

RES VS. TIME POINTS ARE ONLY FOR - ID = 5.00e+00
-5.10e+00
-4.02e+00
-2.94e+00
RES
-1.86e+00
-7.80e-01
3.00e-01
-1.00e+00
4.20e+00
9.40e+00
TIME
1.46e+01
1.98e+01
2.50e+01

Fig. 82

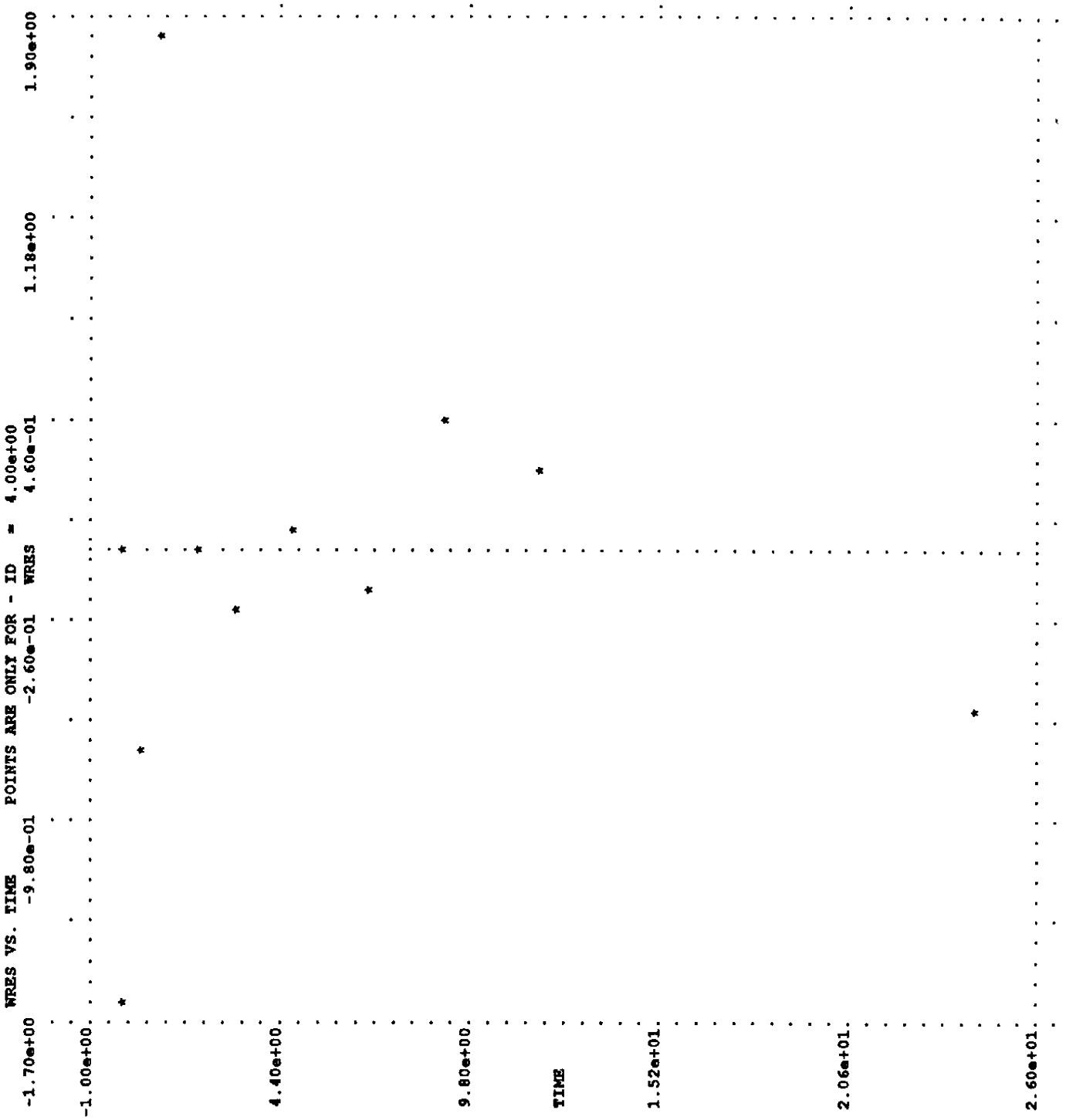
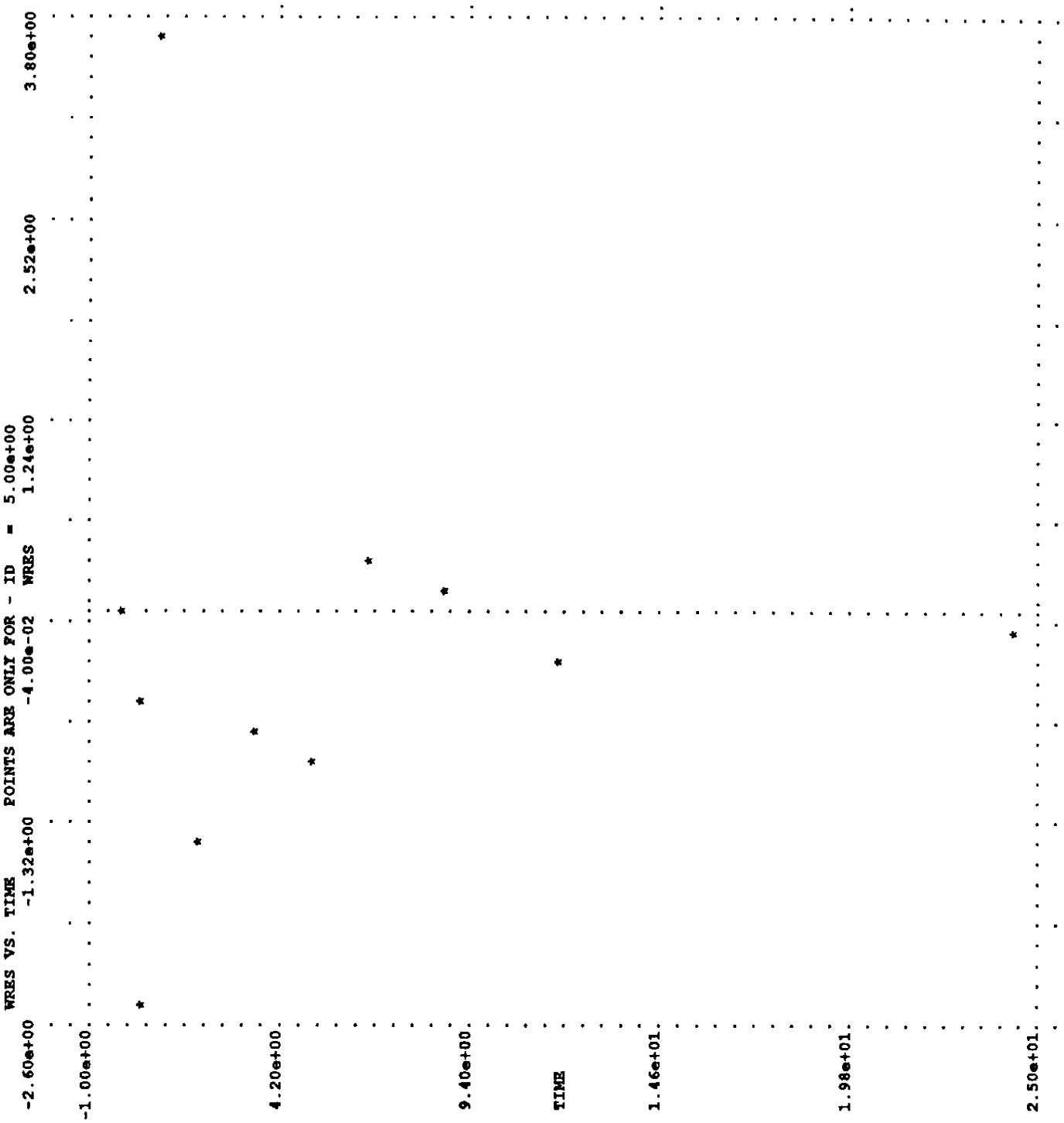

WRES VS. TIME POINTS ARE ONLY FOR - ID = 4.00e+00
-9.80e-01 -2.60e-01 WRES 4.60e-01
-1.70e+00
-1.00e+00
4.40e+00
9.80e+00
1.18e+00
1.90e+00
TIME
1.52e+01
2.06e+01
2.60e+01

Fig. 83


WRES VS. TIME POINTS ARE ONLY FOR - ID = 5.00e+00
-2.60e+00
-1.32e+00
-4.00e-02
1.24e+00
2.52e+00
3.80e+00
WRES
-1.00e+00
4.20e+00
9.40e+00
1.46e+01
1.98e+01
2.50e+01
TIME

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Appendix I. Control Record Formats

Records marked with * may be continued.
The record name, e.g., "INDX", is not repeated on continuation(s).

FILE record (*FILE*) (A4,4X,A72)

Field No.	Value	Function
1	NULL	no file stream
	72 chars	name of file stream

SUPER record (*SUPR*) (A4,4X,I4,I8,I4)

Field No.	Value	Function
1	1-9999	Number of problems in the superproblem
2	2-9999	Number of iterations of the superproblem.
3	0	Input information will be printed for first problem only
	1	Input information will be printed for all problems

PROBLEM record (*PROB*) (A4,4X,A72)

Field No.	Value	Function
1	72 chars	problem heading

DATA record (*DATA*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	data set is embedded in the control stream
	1	data set is in a separate file
	-1	re-use the data set from the previous problem.
2	0 or blank	FORTRAN unit not to be rewound
	1	FORTRAN unit to be rewound
3	0	data set to be read to FINISH record or end of file
	1-9999	no. of data records (low-order digits)
4	1-20	no. of data items per data record
5	0	not data checkout
	1	data checkout only
6	**0-9999**	**no. of data records (high-order digits)** **The no. of data records is Field 6 * 10000 + Field 3.** **When Field 6 is 0 or blank, this is simply Field 3**

ITEM record (*ITEM*) (A4,4X,18I4)

Field No.	Value	Function
1	0-20	index of ID data item
2	1-20	index of DV data item
3	0-20	index of MDV data item
4	0-20	no. of data item indices in INDXS
5	0	no user-supplied labels.
	1	user-supplied labels.
6	0	standard labels PRED,RES and WRES used.
	1	nonstandard labels used.
7	0-20	index of L2 data item
8	0-20	index of first data item specified in CONTR record
9	0-20	index of second data item specified in CONTR record
10	0-20	index of third data item specified in CONTR record
11	0-50	no. of user-supplied labels for tables, scatters
12	0-20	index of MRG_ data item
13	0-20	index of RAW_ data item
14	0-20	no. of items on OMIT record
15	0-20	index of RPT_ data item

INDEX record (*INDX*)* (A4,4X,18I4)

Field No.	Value	Function
1	1-20	1st element of INDXS
2	1-20	2nd element of INDXS
	etc.	

LABEL record (*LABL*)* (A4,4X,9(A4,4X))

Field No.	Value	Function
1	4 chars	label of 1st data item
2	4 chars	label of 2nd data item
	etc.	
m	4 chars	label of last data item
m+1	4 chars	label for PRED (if ITEM(6)=1)
m+2	4 chars	label for RES (if ITEM(6)=1)
m+3	4 chars	label for WRES (if ITEM(6)=1)
m+p+1	4 chars	label for 1st variable in NMPRD4†
m+p+2	4 chars	label for 2nd variable in NMPRD4†
	etc.	
m+p+q	4 chars	label for last displayed variable in NMPRD4

Note
m=no. of data items per data rec.=DATA(4)
p=3 if non-standard labels for PRED, RES, WRES (ITEM(6)=1)
p=0 otherwise
q=no. of user supplied labels for tables, scatters=ITEM(11)
† Blank if this variable is not displayed

OMIT record (*OMIT*)* (A4,4X,18I4)

Field No.	Value	Function
1	4 chars	no. of 1st data item omitted from template matching
2	4 chars	no. of 2nd data item omitted from template matching
	etc.	

FORMAT record (*FORM*) (A4,4X,A72/A80)

Field No.	Value	Function
1	80 chars	format specification (field begins on first continuation record)

FIND record (*FIND*) (A4,4X,18I4)

Field No.	Value	Function
1	0	
2	0	
3	0	No Model specification file (MSFI)
	1	A Model specification file (MSFI) is to be read.
4	0	estimate on file not to be rescaled.
	1	estimate on file to be rescaled.
5	0	No ONLYREAD option
	1	ONLYREAD option

initial STRUCTURE record (*STRC*) (A4,4X,18I4)

Field No.	Value	Function
1	0-70	length of THETA
2	0-70	dimension of OMEGA
3	0-70	dimension of SIGMA
4	blank	
5	blank	
6	0 or blank	OMEGA constrained with a block set partition
	1	OMEGA constrained to be diagonal
7	0 or blank	only if field 6 has value 1
	1-70	number of block sets for OMEGA

If the dimension of SIGMA is 0, the following fields may be ignored.

8	0 or blank	SIGMA constrained with a block set partition
	1	SIGMA constrained to be diagonal
9	0 or blank	SIGMA only if field 8 has value 1
	1-70	number of block sets for SIGMA
10	**blank**	
11	**blank**	
12	**0 or blank**	**default THETA boundary test**
	1	**No default THETA boundary test**
13	**0 or blank**	**default OMEGA boundary test**
	1	**No default OMEGA boundary test**
14	**0 or blank**	**default SIGMA boundary test**
	1	**No default SIGMA boundary test**

STRUCTURE record for OMEGA or SIGMA (*STRC*) (A4,4X,18I4)

Field No.	Value	Function
1	1-70	size of 1st. block set
2	1-70	dimension of blocks in 1st. block set
3	1-70	size of 2nd. block set
4	1-70	dimension of blocks in 2nd. block set
		etc.

THETA CONSTRAINT record (*THCN*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	THETA unconstrained
	1	THETA constrained
2	0 or blank	use default size of initial. est. search
	1-9999	no. of points to be examined during initial est. search.
3	0 or blank	ABORT if PRED sets error return code to 1 during search
	1	NOABORT - Ignore PRED error return code during search
	2	NOABORTFIRST - Same, even with first values.

THETA record (*THTA*)* (A4,4X,9A8)

Field No.	Value	Function
1		initial est. of θ_1
		(blank if NONMEM is to obtain the inital est.)
2		initial est. of θ_2
		(blank if NONMEM is to obtain the inital est.)
	etc.	

LOWER BOUND record (*LOWR*)* (A4,4X,9A8)

Field No.	Value	Function
1		lower bound for θ_1
2		lower bound for θ_2
	etc.	

UPPER BOUND record (*UPPR*)* (A4,4X,9A8)

Field No.	Value	Function
1		upper bound for θ_1
2		upper bound for θ_2
	etc.	

DIAGONAL record (*DIAG*)* (A4,3X,A1,9A8)
for OMEGA or SIGMA

Field No.	Value	Function
Pos. 1	blank	Not fixed.
	1	Fixed.
	2	NONMEM is to obtain the inital estimate(s).
1		initial est. of (1,1) element of matrix
2		initial est. of (2,2) element of matrix
	etc.	

BLOCK SET record (*BLST*)* (A4,3X,A1,9A8)
for OMEGA or SIGMA

Field No.	Value	Function
Pos. 1	blank	Not fixed.
	1	Fixed.
	2	NONMEM is to obtain the inital estimate(s).
1		initial est. of (1,1) element of matrix
2		initial est. of (1,2) element of matrix
	etc.	
		use symmetric enumeration

SIMLUATION record (*SIML*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	Simulation Step implemented
	1	Simulation Step not implemented

If the value is 1, the subsequent fields may be ignored.

2	1-10	no. of random sources (SORC records)
3	0	eta (eps) changes with each record
	1	eta (eps) changes with new ind.rec. (L2 rec) (NEW)
4	0-9999	no. of subproblems
5	0	compute objective function and other steps
	1	only the simulation step
6	0 or blank	no partial derivatives from PRED needed
	1	PRED should compute 1st. derivatives (REQUESTFIRST)
	2	PRED should compute 2nd. derivatives (REQUESTSECOND)
7	0 or blank	simulated observation is Y or F (PREDICTION)
	1	simulated observation is DV (NOPREDICTION)
8	0 or blank	Use inital ests. (TRUE=INITIAL)
	1	with MSFI, use final ests. (TRUE=FINAL)
	2	use values in NMPR16 (TRUE=PRIOR)

SOURCE record (*SORC*) (A4,4X,2A12,I4)

Field No.	Value	Function
1	-1-21474836447	first seed
2	0-21474836447	second seed
3	0 or blank	random numbers are pseudo-normal (NORMAL)
	1	random numbers are pseudo-uniform (UNIFORM)
	2	random numbers are from a nonpar. distrib (NONPARAMETRIC)

ESTIMATION record (*ESTM*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	Estimation Step implemented
	1	Estimation Step not implemented

If the value is 1, the subsequent fields may be ignored.

2	**0-9999**	**maximum no. of function. evaluations (low-order digits)**
	-1	**Reuse the value from the previous run (with MSFI)**
3	1-8	number of significant figs. required in final est.
4	0 or blank	no summarization of iterations
	n > 0	every nth iteration summarized
5	0 or blank	no second search (REPEAT)
	1	second search (REPEAT) implemented
6	0 or blank	MSF not output
	1	MSF output
7	0 or blank	First order (FO) method
	1	Conditional method (METHOD=COND)
8	0 or blank	No POSTHOC etas are to be estimated.
	1	POSTHOC etas are to be estimated.
9	0 or blank	Etas are 0 for comp. of intraind. error (NOINTERACTION)
	1	Nonzero etas for comp. of intraind. error INTERACTION
10	0 or blank	Do not use Laplacian method.
	1	Laplacian method is to be used.
11	0 or blank	ABORT if PRED sets error return code to 1
	1	NOABORT - Attempt theta-recovery when PRED error code 1.
12	0 or blank	Faster method of compuation (NOSLOW)
	1	Slower method of computation (SLOW)
	2	Slower method of computation (SLOW=2); for Stieltjes
13	0 or blank	avg. cond. est. of etas unconstrained (NOCENTER)
	1	avg. cond. est. of etas constrained close to 0. (CENTER)
14	0 or blank	First-order model not used (NOFO)
	1	First-order model used with METHOD=1 CENTERING (FO)
15	0 or blank	Second eta-derivs. computed by PRED (NONUMERICAL)
	1	Second eta-derivs. for Laplacian to be obtained numerically.
16	0 or blank	Y or F (with user-supplied code) is a prediction.
	1	Y or F is a LIKELIHOOD.
	2	Y or F is a -2LOGLIKELIHOOD
17	0 or blank	Not the Hybrid method
	1-99	no. of etas fixed to zero by ZERO recs. (Hybrid method)
18	0 or blank	Not the Stieltjes method.
	1	Stieltjes method; no GRID option.
	2	Stieltjes method; GRID was specified.

ESTIMATION rec. continuation rec. ( ) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	Required if estimation step is omitted, otherwise:
	0 or blank	The REPEAT2 option is not coded; same as NOREPEAT2
	1	REPEAT2 (with Stieltjes)

2	0 or blank	No ETABARCHECK.
	1	ETABARCHECK option is coded.
3	0 or blank.	Sum contrib. to obj. func. in data set order.
	1	Sort contrib. to obj. func. prior to sum (SORT)
4	**0-9999**	**maximum no. of function evaluations (high-order digits)**
		The no. of func. evals. is Field 4 * 10000 + low-order
		When Field 4 is 0 or blank, this is simply low-order

ZERO record (*ZERO*)* (A4,4X,18I4)

Field No.	Value	Function
1	0	conditional estimate for eta(1)
	1	eta(1) is fixed to 0 (HYBRID method)
2	0	conditional estimate for eta(2)
	1	eta(2) is fixed to 0 (HYBRID method)
	etc.	

GRID record (*GRID*) (A4,4X,9A8)

Field No.	Value	Function
1	nr	as specified in GRID=(nr,ns,r0,r1)
2	ns	as specified in GRID=(nr,ns,r0,r1)
3	r0	as specified in GRID=(nr,ns,r0,r1)
4	r1	as specified in GRID=(nr,ns,r0,r1)

NONPARAMETRIC record (*NONP*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	Nonparametric step implemented conditionally
	1	Nonparametric step implemented unconditionally
2	0 or blank	use nonparametric estimate from input MSF
	1	recompute nonparametric estimate
3	0 or blank	obtain marginal cumulatives
	1	compute conditional nonpar. etas (CNPE ETAS)
4	0 or blank	no model specification file is output
	1	a model specification file is output

COVARIANCE record (*COVR*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	Covariance Step conditionally implemented
	(1)	(Covariance Step unconditionally implemented - obsolete)
	2	Covariance Step not implemented
2	0 or blank	covariance matrix set to (R inverse) S (R inverse)
	1	covariance matrix set to R inverse
	2	covariance matrix set to S inverse
3	0 or blank	neither R nor S printed.
	1	R matrix printed
	2	S matrix printed
	3	both R and S printed
4	0 or blank	eigenvalues not printed
	1	eigenvalues printed.
5	0 or blank	default computation.
	1	Special computation with a recursive PRED subroutine.
6	0 or blank	Print Covariance Step arrays in normal format.
	1	Print Covariance Step arrays in compressed format.
7	1	
8	0 or blank	
9	0 or blank	Normal method of computation
	1	Slower method of computation (SLOW)

initial TABLE record (*TABL*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	Table Step conditionally implemented
	1	Table Step unconditionally implemented
	2	Table Step not implemented

If the value is 2, the next field may be ignored, and there should not appear any individual TABLE records.

2	1-10	number of tables

individual TABLE record (*TABL*) (A4,3X,I1,18I4)

Field No.	Value	Function
Pos. 1	blank	no option record.
	1	an option record follows.
		(only if at least one item on the option rec. is non-blank)
1	0-50	number of selected data item types
2	1-999	index of 1st selected data item type
3	0-8	sort code for data items of 1st selected type
4	1-999	index of 2nd selected data item type
5	0-8	sort code for data items of 2nd selected type
	etc.	

individual TABLE rec. contin. rec. ( )* (A4,4X,18I4)
(as needed)

Field No.	Value	Function
1	1-999	index of 9th. selected data item type
2	0	
3	1-999	index of 10th. selected data item type
4	0	
	etc.	

individual TABLE record option rec. ( ) (A4,4X,18I4)

Field No.	Value	Function
1	blank	Every data record appears in the table.
	1	Only the first data rec. from each ind. rec. (FIRSTONLY)
2	1	With TABLE file, no printed table (NOPRINT)
	2	With TABLE file, printed table appears in the NONMEM output.
3	blank	Normal header lines appear in the TABLE file.
	1	Only one header in the TABLE file (ONEHEADER)
	2	No headers are included in the TABLE file (NOHEADER)
4	blank	The TABLE file is opened and is positioned at the start.
	1	The TABLE file is positioned at the end (FORWARD)
5	blank	DV, PRED, RES, WRES appear automatically
	1	DV, PRED, RES, WRES do not appear unless listed (NOAPPEND)

initial SCATTERPLOT record (*SCAT*) (A4,4X,18I4)

Field No.	Value	Function
1	0 or blank	Scatterplot Step conditionally implemented
	1	Scatterplot Step unconditionally implemented
	2	Scatterplot Step not implemented

If the value is 2, the next field may be ignored, and there should not appear any individual SCATTERPLOT records.

2	1-20	number of families

individual SCATTERPLOT record (*SCAT*) (A4,4X,6I4,2I8,4I4,16X)

Field No.	Value	Function
1	1-23	index of data items plotted on abcsissa axis
2	1-23	index of data items plotted on ordinate axis
3	0 or blank	a single scatterplot
	1	a one-way partitioned scatterplot
	2	a two-way partitioned scatterplot

If the value of field 3 is 0 or blank, the next two fields should be ignored.

4	1-23	index of 1st separator

If the value of field 3 is 1, the next field should be ignored.

5	1-23	index of 2nd separator
6	0 or blank	no unit slope line appears
	1	unit slope line appears
7	0-99999999	no. of the first data rec. for the scatter (FROM)
8	0-99999999	no. of the last data rec. for the scatter (TO)
9	0 or blank	a line through zero on the ordinate axis if appropriate.
	1	a line through zero on the ordinate axis. (ORD0)
	-1	no line through zero on the ordinate axis.
10	0 or blank	a line through zero on the abscissa axis if appropriate.
	1	a line through zero on the abscissa axis. (ABS0)
	-1	no line through zero on the abscissa axis.
11	0 or blank	Every data record appears in the scatter.
	1	Only the first data rec. from each ind. rec. (FIRSTONLY)
12	0 or blank	Every data record appears in the scatter
	1	Only data records with MDV=0 (OBSONLY).