Chapter 12 - Brief Descriptions of Other Features

1. What This Chapter is About

This chapter briefly describes a variety of features of PREDPP and NONMEM that are somewhat advanced for this text but are of interest to most users of NONMEM. References are given to other documents where additional information can be found. Section 2 is concerned with PREDPP, Section 3 is concerned with user-written PREDs, and Section 4 describes general NONMEM features. Section 5 contains an example that includes several of the advanced features. Descriptions of NM-TRAN control records in Section 4 have been augmented with sections headed "More about ...". These contain additional details, plus new options for NONMEM 7.3. Section 6 is new for NONMEM 7.3. It contains a supplemental list of features through NONMEM 7.3, including features from previous releases that are not otherwise discussed in this guide.

Note that wherever $PK, $ERROR, $DES, $AES, $MODEL, $MIX, $INFN and $PRED statements are referred to below, user-written subroutines PK, ERROR, DES, AES, MODEL, MIX, INFN and PRED can be used instead.

2. Advanced Features of PREDPP

2.1. Pharmacodynamic Modeling Using the $ERROR Record

$ERROR statements may modify the value of F, the scaled drug concentration. They may also introduce new θ and η variables. This allows pharmacodynamic modeling to be performed using PREDPP. Such models occur when a study involves measurement of a drug effect, such as blood pressure. A proposed model might relate the predicted effect to a pharmacokinetic quantity such as plasma level. PREDPP can be used to model C_p as is usual, and the predicted effect can be computed in the $ERROR statements.

For example, suppose that a modified version of the phenobarbital data of Chapter 2 includes observations of some drug effect (in this case, perhaps a measure of the degree of sedation) but none of the concentration observations. The dose event records are the same as those of the earlier example. Suppose that the drug concentrations from each individual have been used to estimate that individual's K and V parameters, and that these estimates are now included on every event record for the individual. Finally, suppose that the proposed structural model for the effect, E, is an "E-max" model:

$$E = E_{\max} \frac{C_p}{C_{50} + C_p}$$

where here C_p is understood to mean the prediction of an individual's drug concentration in the plasma, and $E_{\max}$ and C_{50} are PD (pharmacodynamic parameters) modeled as

$$E_{\max} = \theta_1 + \eta_1$$

$$C_{50} = \theta_2 + \eta_2$$

To fit this data we can use the control statements of figure 12.1. To obtain initial parameter estimates, let us assume that the following is observable in the data. The average value of all effect measurements is about 50. Across individuals, the average value of the largest effect measurement within each individual's data is about 100, and the average value of the individual's observed concentration at about half this largest measurement is about 20. (This is seen when concentration measurements and effect measurements are examined together.) Let us also assume 20% random interindividual variability in $E_{\max}$ and C_{50} and 4% intraindividual variability in the observation. From this we obtain initial estimates of 100 and 20 for θ_1 and θ_2, $(100\times.2)^2$ for Ω_{11}, $(20\times.2)^2$ for Ω_{22}, and $(50\times.04)^2$ for Σ.

This example is examined again in in Section 3.2, which shows the use of $PRED statements, and in Section 5, which shows how observed concentrations and effects can be fit simultaneously.

References: Users Guide VI (PREDPP) IV.B.2

```
$PROBLEM PHARMACODYNAMIC MODEL USING $ERROR STATEMENTS
```

```
$INPUT   ID TIME AMT INDK INDV DV
$DATA    EFFDATA
$SUBROUTINE ADVAN1
$PK
   K=INDK
   V=INDV
   S1=V
$ERROR
 EMAX=THETA(1)+ETA(1)
 C50=THETA(2)+ETA(2)
 E=EMAX*F/(C50+F)
 Y=E+ERR(1)

$THETA   100  20
$OMEGA   400  16
$SIGMA   4
$ESTIMATION
```

Figure 12.1. The input to NONMEM-PREDPP for analysis of effect observations.

2.2. Other Pharmacokinetic Models: ADVAN5 through ADVAN9 and ADVAN13

Appendix 1 lists ADVAN routines for the most commonly-used pharmacokinetic models. Other ADVAN routines are:
ADVAN5 (General Linear)
ADVAN6 (General Nonlinear)
ADVAN7 (General Linear with Real Eigenvalues)
ADVAN8 (General Nonlinear Kinetics with Stiff Equations)
ADVAN9 (General Nonlinear Kinetics with Equilibrium Compartments)
ADVAN13 (General Nonlinear Kinetics using LSODA)

With the general methods the user defines a model of up to 999 compartments using special options of the $MODEL record. For a linear model (ADVAN5 and ADVAN7), it is sufficient to specify (directed) compartmental connections and to compute their rate constant parameters with $PK statements. ADVAN 5 and 7 make use of numerical approximations to the matrix exponential. For a nonlinear model (ADVAN6, ADVAN8, ADVAN9, and ADVAN13), differential equations must be supplied to govern the kinetics, via $DES statements. It is possible to specify initial conditions for the differential equations using the I_SS (Initial Steady State) feature; Reserved variable ISSMOD may be used.

For ADVAN9, algebraic equations may also be supplied via $AES statements.

The use of the term 'nonlinear' with ADVAN 6, 8, 9, and 13 only indicates that a system of any type of first-order differential equations is allowed; such equations could be linear or non-linear.

In all cases, the basic features of PREDPP described in Chapter 7 are still available, such as the ability to introduce doses of any kind to any compartment of the model. It should be noted that the general ADVAN routines are relatively slow. For example, when a general method is used for a model identical to that of an analytic method (ADVAN1 through ADVAN4 or ADVAN10 through ADVAN12) the run time increases, usually by an order of magnitude.

Some ADVAN and SS routines must be told the number of accurate digits that are required in the computation of drug amounts, i.e., the relative tolerance. This is specified either by the TOL option of the $SUBROUTINES record or by the $TOL record. Option TOL may also be specified on $ESTIMATION and $COVARIANCE records. With ADVAN9 and ADVAN13, option ATOL (absolute tolerance) may also be specified on $ESTIMATION and $COVARIANCE records.

With ADVAN9 and ADVAN13, reserved variable MXSTEP may be used to set the number of integration steps.

With $AES, $AESINIT statements are also required. If there is no TIME data item, $AESINIT may specify a calling protocol for the AES subroutine. (See 2.7 below for a discussion of calling protocols.)

`CALLFL=-1`:
Call ADVAN9 and AES with every event record (default)

`CALLFL=1`:
Call ADVAN9 and AES once per individual record.

Equivalent calling protocol phrases are:

```
(EVERY EVENT)
(ONCE PER IR)
```

References: Users Guide VI (PREDPP) VI, VII
References: Users Guide IV (NM-TRAN) V.C.3, 4, 7-10

2.3. Zero-Order Bolus Doses

Instantaneous bolus doses, which have AMT>0 and RATE=0, are described in Chapter 6. Such doses appear instantaneously in the dose compartment. Zero-order bolus doses are doses that enter the dose compartment via a zero-order process (in the same manner as do infusions) except that the rate or duration of the process is computed with $PK statements. When the RATE data item has the value -1, then the $PK statements must include an assignment statement for an additional PK parameter, Rn (the "modeled rate for compartment n"), whose value gives the rate of entry of the drug during the interval of time between the last event record and the current one. There is a different such parameter for every compartment receiving a zero-order bolus dose. When the RATE data item has the value -2, then the $PK statements must include an assignment statement for an additional PK parameter, Dn (the "modeled duration for compartment n"), whose value at the time of the dose event gives the duration time of the dose. The rate and duration parameters can be modeled like any other PK parameters; in particular, the assignment statements can involve θ's which are to be estimated. These parameters can be used to model the drug release rate or dissolution time of a tablet or capsule.

Steady-state levels involving zero-order bolus doses can be computed.

Steady-state with constant infusion was described in Chapter 6. Steady-state infusions may also have modeled rates (i.e., the RATE data item may be -1).

References: Users Guide VI (PREDPP) III.F.3, F.4

2.4. The Additional Dose Data Item: ADDL

ADDL is a dose-related data item that is used to request that a given number of additional doses, just like the dose specified on the event record, be added to the system at a regular time interval, starting from the time on the event record. PREDPP itself adds these doses at the appropriate future times; no actual dose event record is generated by the Data Preprocessor or by PREDPP. A positive integer value in ADDL specifies how many additional doses (i.e., in addition to that already specified in the event record) are to be given, and the value in the II (interdose interval) data item (which is required) specifies the time interval between doses.

ADDL may be non-zero on a steady-state dose event record (except for steady-state infusions), in which case additional doses are given, maintaining the dosing regimen into the future. Non-steady-state kinetic formulas are used to advance the system between each additional dose. Reserved variables DOSTIM (the time of a lagged dose or additional dose to which the system is being advanced) and DOSREC (the dose record corresponding to the dose entering at DOSTIM) may be used.

See also Section 2.6 below.

References: Users Guide VI (PREDPP) V.K

2.5. Lagged doses: the ALAG Parameter

PREDPP permits an additional PK parameter called an absorption lag time. One such parameter can be defined for each compartment and applies to all doses to that compartment. It gives the amount of time that a dose is held as a "pending" dose. When the absorption lag time has expired, the dose is input into the system. In effect, the value of the absorption lag time parameter is added to the value of the TIME data item on the dose event record. With NM-TRAN, recognized names for absorption lag time parameters have the form ALAGn, where n is the compartment number. Reserved variables DOSTIM (the time of a lagged dose or additional dose to which the system is being advanced) and DOSREC (the dose record corresponding to the dose entering at DOSTIM) may be used.
See also Section 2.6 below.

References: Users Guide VI (PREDPP) III.F.6
References: Users Guide IV (NM-TRAN) V.C.5

2.6. Model Event Times: MTIME

Model event times MTIME(i) are additional PK parameters defined in the PK routine or $PK block. A model event time is not associated with any compartment, but, like an absorption lag time, defines a time to which the system is advanced. When the time is reached, indicator variables are set and a call to PK is made. At this call (and/or subsequent to this call) PK or DES or AES or ERROR can use the indicator variables to change some aspect of the system, e.g., a term in a differential equation, or the rate of an infusion. Reserved variables MNEXT, MPAST, MNOW, MTDIFF may be used.

2.7. Controlling Calls to PK and ERROR

In order to evaluate the $PK and $ERROR statements, PREDPP calls the PK and ERROR subroutines. By default, the subroutines are called with every event record. PREDPP may be instructed to limit calls to certain event records in order to save the computing time involved with unnecessary calls (e.g. when the PK parameters do not vary from event record to event record within an individual). It is also possible to cause the PK subroutine to be called at times which do not correspond to any actual event record.

Using NM-TRAN, calls to PK are controlled by the presence of one of the following pseudo-statements, at the start of the $PK block:

`CALLFL=-2`:
: call with every event record, at additional and lagged dose times, and at modeled event times.

`CALLFL=-1`:
: call with every event record (default).

`CALLFL=0`:
: call with the first event record of each individual record and with new values of TIME.

`CALLFL=1`:
: call once per individual record.

A calling protocol phrase may be used instead of a pseudo-statement. A calling protocol phrase may use upper- or lower-case characters. It must be enclosed in parentheses. NM-TRAN can understand minor variations in the wording. E.g., the word "CALL" and prepositions such as WITH can be omitted. Here are calling protocol phrases equivalent to the above four pseudo-statements,

respectively.

```
(CALL WITH NON-EVENT TIMES)
(CALL WITH EVERY EVENT RECORD)
(CALL WITH FIRST EVENT RECORD AND NEW TIME)
(CALL ONCE PER INDIVIDUAL RECORD)
```

The choice `CALLFL=-2 (CALL WITH NON-EVENT TIMES)` is intended to be used when PK parameters Dn and/or Fn apply to additional or lagged doses *and* the model for these parameters depends on some time-varying concomitant variable such as type of drug preparation or patient weight. By default, the values of the PK parameters which apply to the dose are those values computed by PK with the first event record having a value of TIME greater than the time at which the dose actually enters the system (the additional or lagged dose time). However, if PREDPP is instructed to also call PK at the additional or lagged dose time, then the values of the PK parameters are those values computed at these special calls. At such calls, PK has available to it information from the initiating dose event record itself, and information from the two event records whose TIME values bracket the additional or lagged dose time. Along with `CALLFL=-2` in the $PK block, the NM-TRAN $BIND record may be useful; see Users Guide IV.

Using NM-TRAN, calls to ERROR are controlled by the presence of one of the following pseudo-statements at the start of the $ERROR block:

`CALLFL=-1`:
call with every event record (default).

`CALLFL=0`: call with observation events only.

`CALLFL=1`: call once per individual record.

A calling protocol phrase may be used instead of a pseudo-statement. As in the $PK block, the calling protocol phrase may use upper- or lower-case characters and must be enclosed in parentheses.

Here are calling protocol phrases equivalent to the above three pseudo-statements, respectively.

```
(CALL WITH EVERY EVENT RECORD)
(CALL WITH OBSERVATION EVENTS)
(CALL ONCE PER INDIVIDUAL RECORD)
```

NM-TRAN automatically instructs PREDPP to limit calls to ERROR to once per *problem* for the simple error models discussed in Chapter 8, Sections 3.1 and 3.2:

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

During the Simulation Step, PREDPP ignores any limitation and calls the ERROR subroutine with every event record.

Even when calls to PK and/or ERROR are limited, the CALL input data item can be used to force additional calls for specific event records as needed.

References: Users Guide VI (PREDPP) III.B.2, III.H, IV.C, V.J
References: Users Guide IV (NM-TRAN) V.C.5, C.6

2.8. Transgeneration of Input Data: the INFN Subroutine

NONMEM may be used to modify the data records before any computations are performed and also after all computations have been performed. This is referred to as transgeneration of the data. Transgeneration at the beginning of a problem can be used, for example, to change weight-normalized doses to unnormalized doses. PREDPP allows the user to supply a subroutine called

INFN or a $INFN block of abbreviated code ("initialization/finalization") in which transgeneration can be performed. (The PREDPP library includes a default INFN subroutine which does nothing.)

The NONMEM PASS subroutine is used for transgeneration. $INFN and $PRED code may use the following statements to process each record of the data set. ICALL values may be 0, 1 or 3, for run initializaton, problem initialization, and problem finalization, respectively.

```
IF (ICALL == 3) THEN
DOWHILE(DATA)
  ...
ENDDO
ENDDO
```

Reserved variable PASSRC may be of interest.

References: Users Guide VI (PREDPP) VI.A

3. User-written PRED Subroutines

It is not necessary to use PREDPP with NONMEM. Either $PRED statements or a user-written PRED subroutine may be used in place of PREDPP to supply NONMEM with predicted values for the DV data item according to some (not necessarily pharmacokinetic) model. An example using $PRED statements is given here. A special caveat applies to user-written PRED subroutines that are recursive: see 4.6 below.

References: Users Guide I (Basic) C.2

3.1. Required Data Items

The only required data items when PREDPP is not used are the NONMEM data items DV, MDV, and ID. When PREDPP is used, the Data Preprocessor is able to recognize which records contain observed values and which do not, and it supplies the MDV data item if it is not already present in the data file. When PREDPP is not used, the Data Preprocessor cannot do this. The input data file must already contain the MDV data item if it is needed, i.e., if the DV item of some data record does not contain a value of an actual observation.

If $PRED statements are used, they must calculate a variable called Y, using input data items and NONMEM's θ, η, and (for population models) ε vectors in the calculation.

References: Users Guide I (Basic) B.1
References: Users Guide IV (NM-TRAN) III.B.8

3.2. An Example of $PRED Statements: Pharmacodynamic Modeling

The syntax of $PRED statements is essentially the same as discussed for $PK and $ERROR statements. $PRED statements can be used for simple pharmacokinetic and pharmacodynamic models. In figure 12.1 above an example was given of pharmacodynamic modeling using $ERROR statements. Suppose that in that example, drug concentration is always measured at the same time as drug effect. Suppose too, that rather than input the individuals' values of K and V and use them to compute a predicted drug concentration for the individual, the observed drug concentration itself is used in the Emax model. This means that the the observed concentrations are again incorporated into the data, but now as values of an independent variable, rather than as the DV data item. This also means that a pharmacokinetic model is not needed, and therefore, PREDPP is not needed either. Figure 12.2 shows the control stream for this new example.

```
$PROBLEM A SIMPLE PHARMACODYNAMIC MODEL
$INPUT   ID TIME CP DV
$DATA    EFFDATA
```

```
$PRED
 EMAX=THETA(1)+ETA(1)
 C50=THETA(2)+ETA(2)
 E=EMAX*CP/(C50+CP)
 Y=E+ERR(1)
$THETA   100   20
$OMEGA   400   16
$SIGMA   4
$ESTIMATION
```

Figure 12.2. The input to NONMEM including $PRED statements for analysis of effect data.

4. Advanced Features of NONMEM

4.1. Full Covariance Matrices: $OMEGA BLOCK and $SIGMA BLOCK

In the examples of Chapter 2 and 9, there appeared statements such as:

```
$OMEGA  .0000055, .04
```

This is an example of the specification of initial parameter estimates for a variance-covariance Ω matrix which is constrained to be *diagonal*. Initial estimates are given for the variances of η_1 and of η_2. The covariance between η_1 and η_2 is constrained to be 0, i.e., $\omega_{12} = cov(\eta_1, \eta_2) = 0$. Another way of writing this statement is:

```
$OMEGA DIAGONAL(2)  .0000055, .04
```

The option `DIAGONAL(2)` states explicitly that the block contains two ηs and that it has diagonal form.

If the data supports the possibility that η_1 and η_2 covary with each other, it may be useful to model Ω as being unconstrained and allow NONMEM to estimate the covariance. A special form of the $OMEGA record is used, in which initial values are supplied for both variances and the covariance. For example:

```
$OMEGA BLOCK(2)  .0000055, .0000001, .04
```

The option `BLOCK(2)` states that there are two η variables in the block, and that covariance is to be estimated. The new element is $\omega_{12} = \omega_{21} = cov(\eta_1, \eta_2) = cov(\eta_2, \eta_1) = 1 \times 10^{-7}$.

$OMEGA BLOCK is used for both population and individual studies, i.e., it is the same whether η is used in the first case in a model for residual error or is used in the second case in a model for random interindividual error. In a population study, if there is more than one ε variable, and the model allows these variables to covary, then $SIGMA BLOCK is used in a similar manner.

The initial estimates of even more complicated Ω and Σ matrices may be given using multiple $OMEGA and $SIGMA records. For example, the initial estimates of a mixture of correlated and uncorrelated random variables may given. Also, in this context (as with the simple form of the $OMEGA and $SIGMA records described in Chapter 9, Section 3) variances-covariances may be constrained to fixed values by means of the FIXED option. Finally, some variances-covariances may be constrained to equal others by means of the BLOCK SAME option.

The ability to fix all variances-covariances in both Ω and Σ allows Bayesian estimates to be obtained of the pharmacokinetic parameters of a single individual, based on the individual's data and a prior population distribution for the parameters.

References: Users Guide IV (NM-TRAN) III.B.10

4.1.1. More About $OMEGA and $SIGMA

Initial estimates of a block of $OMEGA or $SIGMA must be positive definite unless the entire block is fixed to 0.

If initial estimates of a block of $OMEGA or $SIGMA is not positive definite because of rounding errors, a value will be added to the diagonal elements to make it positive definite. A message

in the NONMEM report file will indicate if this was done. (nm73).

Additional options include:
`VARIANCE` (initial estimates of diagonal elements are variances (default))
`STANDARD` or `SD` (initial estimates of diagonal elements are standard deviations)
`COVARIANCE` (initial elements of off-diagonal elements are covariances (default))
`CORRELATION` (initial elements of off-diagonal elements are correlation)
`CHOLESKY` (the block is specified in its Cholesky form)

NONMEM converts all initial estimates to variance and covariances. The values desplayed in the NONMEM report and in the raw and additional output files are always variances and covariances.

If the initial estimate of $OMEGA or $SIGMA has band-symmetric form, NONMEM will be constrained to retain this form (nm7).

Special value of $OMEGA element for single-subject analysis: If all diagonal elements of $OMEGA are "1.0E+06 FIXED" this indicates that, in a multi-subject data set, each subject's data is to be analyzed as individual data. This is the alternate method ("TYPE2") for single-subject analysis (nm73)

Short-cuts may be used for entering repeated information.

BLOCK SAME(m) option
: A count m may be included. With `$OMEGA BLOCK(n) SAME(m)` the `$OMEGA BLOCK(n) SAME` record is repeated m times. Similarly for $SIGMA records (nm73).

$THETA, $OMEGA, $SIGMA Repeated values
: When specifying initial estimates, a repeated value can be coded using notation (...)xn. E.g., $OMEGA (2)x4 can be used in place of $OMEGA 2 2 2 2. Simliarly for $SIGMA and $THETA.

$OMEGA,$SIGMA VALUES option
: If initial estimates of all diagonal elements of $OMEGA or $SIGMA are the same, and initial estimates of all off-diagonal elements are the same, they can be specified simply as $OMEGA BLOCK(n)VALUES(diag,odiag).

Informative record names for `$OMEGA` and `$SIGMA` may be used to make it easier place the records in the control stream.

`$OMEGAP` specifies omega priors
`$OMEGAPD` specifies degrees of freedom (or dispersion factor) for omega priors

They are identical to `$OMEGA` records, but understood to specify prior information for NWPRI. They may be placed anywhere in the control stream, whereas the same records without "P" or "PD" would have to be in a specific location.

Informative record names `$SIGMAP` and `$SIGMAPD` may be used similarly.

4.2. Grouping Related Observations: The L1 and L2 Data Items

The $ERROR statements for a problem may sometimes involve more than one random variable. For example, there may be two types of observations. One type may be an observation from one compartment of a PK system, or with one assay or preparation, and another type may be an observation from a different compartment or with a different assay or preparation. The model for the two types of observations would typically involve at least two *eps* variables (e.g. (3.8)). If all observations are made at sufficiently separated times, there may be little reason to be concerned about correlation between the two random errors. However, if the two types of observations are taken at the same or very close to the same time, it is possible that correlation will exist; whatever

circumstance has influenced one observation to be different from the predicted level may also have some influence on the other observation. In this case a covariance between the two *eps* variables should be allowed, as described above in Section 4.1. Then the two types of observations at the same time point are regarded as two elements of a multivariate observation.

In the case of population data, there exists a NONMEM data item, L2, which is used to identify the elements of a multivariate observation. In effect, L2 acts in a similar way as ID, but grouping observations *within* individual records.

In the case of individual data, the ID data item already serves this purpose: it forms groups of observations whose η variables may be correlated. Thus, in the input data file, the ID data item should be the same for those observations which may have correlated ηs. However, for individual data, the Data Preprocessor normally replaces the ID data item with a new set of values which describe every observation as being independent of the others. To prevent the Data Preprocessor from doing this, L1 should be included in the $INPUT record as the name or synonym for the user-supplied ID data item.

Auto-correlation: The values of epsilons used in the intraindividual model may be correlated across the observations contained in the L2 record. Auto-correlation may be part of both Simulation and Estimation. The CORRL2 reserved variable may be used.

References: Users Guide IV (NM-TRAN) II.C.4, III.B.2
References: Users Guide II (Supplemental) D.3

4.3. Continuing a NONMEM Run: MSFO and MSFI

The `MSFO` (Model Specification Output File) option of the $ESTIMATION record instructs NONMEM to write a Model Specification File (MSF). It is created when NONMEM writes the first iteration summary to the intermediate output file, and is re-written when every subsequent iteration summary is written. This file can then be read in a subsequent NONMEM run using a $MSFI (Model Specification File Input) record. This file has much of the information about the model used in the previous run, thus the name "Model Specification File". It also contains all the information that allows the Estimation Step from the previous run (which may have terminated, for example, due to the number of function evaluations exceeding its limit or a computer crash or some other externally-caused interruption of the NONMEM run) to be continued in the subsequent run. There are a number of benefits to using a MSF. First, what might be a long Estimation Step (due to a very lengthy search) can be split over a series of runs, each with a limited number of function evaluations. Any run which terminates prematurely due to computer failure can be restarted from the MSF output in the previous run. (This provides a "checkpoint/restart" capability.) The progress made in the Estimation Step can also be evaluated between runs, and a decision made as to whether it is worth continuing a search which is consuming excessive amounts of computer time. Second, the Covariance, Tables, and Scatterplot Steps can be performed in later runs, each using the MSF from the final run with the Estimation Step. It is advisable to perform the Covariance Step only after satisfactory results have been obtained from the Estimation Step. Third, when NONMEM writes to the MSF, it also writes iteration summaries to the intermediate printout file (INTER). These iteration summaries are in the original parameterization (nm72).

References: Users Guide I (Basic) C.4.4
References: Users Guide IV (NM-TRAN) III.B.6, B.12

4.4. NONMEM Can Obtain Initial Estimates for θ, Ω, Σ

NONMEM can be directed to obtain initial estimates for one or more elements of θ, Ω, or Σ. This is done in a separate Initial Estimates Step. For an element of θ, omit the initial estimate but include lower and upper bounds, e.g., (1, ,50) in the $THETA record. (The NUMBERPOINTS

option may be used to control the number of points in θ space examined by NONMEM during the search for initial estimates of θ.) For a block of Ω or Σ, omit all initial estimates on the $OMEGA BLOCK (or DIAGONAL) record, or $SIGMA BLOCK (or DIAGONAL) record, respectively.

Note that when $PK and $ERROR statements are present but the $OMEGA and/or $SIGMA records are absent, NONMEM will be directed to obtain initial estimates for the variances of the random variables in question, assuming the diagonal form of the matrix.

References: Users Guide IV (NM-TRAN) III.B.9-11

4.5. Improving Parameter Estimates: REPEAT and RESCALE

The Estimation Step can be immediately repeated after the search has terminated successfully, by including the `REPEAT` option on the $ESTIMATION record. This can improve the accuracy of the parameter estimates when one or more initial estimates are wrong by a few orders of magnitude. The final estimates from the first implementation of the Estimation Step are used as the initial estimates of the second implementation, and thus the scaling used with the STP is different from that with the first implementation, allowing fewer leading zeros after the decimal point in the STP. When the Estimation Step is continued by means of a Model Specification File, similar rescaling can be requested using the `RESCALE` option of the $MSFI record.

References: Users Guide IV (NM-TRAN) III.B.12, B.14
References: Users Guide II (Supplemental) F

4.6. The Covariance Step: $\mathbf{R^{-1}}$, $\mathbf{S^{-1}}$, Special Computation

The Covariance Step, which computes standard errors of the parameter estimates, first computes a covariance matrix of the parameter estimates. (This is not the same as the Ω or Σ matrix). It is possible to request that this covariance matrix be computed in one of three different ways: either as R^{-1}, S^{-1}, or $R^{-1}SR^{-1}$ (the default), where R and S are two matrices from statistical theory, the Hessian and Cross-Product Gradient matrices, respectively. Options `MATRIX=R` and `MATRIX=S` of the $COVARIANCE record are used to request the R^{-1} and S^{-1} matrices, respectively. The Covariance Step can produce additional output. When the default covariance matrix is used, R^{-1} and/or S^{-1} can be printed. This is requested by options `PRINT=R` and/or `PRINT=S`. Eigenvalues are be printed if requested by option `PRINT=E`. Multiple `PRINT` options can be specified.

A special computation is *required* when the data are from a single individual and a recursive PRED is used. A recursive PRED is one which stores the results of certain computations using the values from one event record, and uses these results in later computations with the values from a later event record. PREDPP advances the kinetic system from one time point to the next and therefore is an example of a recursive PRED. When PREDPP is used and the data is from a single individual, NM-TRAN automatically requests the special computation. When a recursive user-written PRED is used and the data are from a single individual, the `SPECIAL` option of the $COVARIANCE record *must* be used.

The `CONDITIONAL` option of the $COVARIANCE record requests that the Covariance Step be implemented only if Estimation Step terminates successfully, and is the default. The `UNCONDITIONAL` option can be used to request that it be implemented no matter how the Estimation Step terminates.

References: Users Guide IV (NM-TRAN) III.B.15
References: Users Guide II (Supplemental) D.2.5

4.6.1. More About $COVARIANCE

Other options of interest:

`COMPRESS` (affects how the Covariance matrices are displayed in the NONMEM report)
`NOSLOW | SLOW` (SLOW Requests a slower method of computation)
`SIGL | SIGLO` (affects how computations are done in the Covariance Step)
`RESUME` (allows the Covariance Step to resume from a MSF)
`NOFCOV` (turns of the Covariance Step for Estimation steps using the classical methods)

The $ESTIMATION record option NOCOV may be used to turn off the Covariance Step following a particular Estimation step, and to turn it back on again.

4.7. Multiple Problems in a Single NONMEM Run

NONMEM can implement more than one problem in a single run. That is, the input control stream can contain more than one $PROBLEM record, each followed by its own set of problem specification statements. This feature can be useful in a variety of situations. A series of what otherwise would be separate runs, each analyzing a single individual's data within a population data file, can be performed conveniently without building separate data files for each individual. Also, more than one data set can be analyzed using the same model and the same problem specification. Multiple problems are also useful with NONMEM's Simulation Step, described below.

Note that abbreviated code such as $PK and $ERROR statements cannot appear after the first problem. If the $DATA record is omitted or the filename is specified as * on a $DATA record in a problem subsequent to the first, the previous data set is re-used.

With multiple problems, the following NONMEM reserved variables are of interest:
NPROB,IPROB

A sequence of problems may be defined to be a superproblem by means of the NM-TRAN $SUPER record, and NONMEM may also be directed to repeat them a specific number of times.

With superproblems, the following NONMEM reserved variables are of interest:
S1NUM S2NUM S1NIT S2NIT S1IT S2IT
SKIP_ variable for Superproblem termination

References: Users Guide IV (NM-TRAN) III.B.1

4.8. Simulation Using NONMEM: The $SIMULATION Record

The term simulation refers to the generation of data points according to some model. A simple form of simulation is performed when the Estimation Step is omitted but the Table Step is implemented. The PRED column of the table contains predictions based on the information in the data records and the initial estimates of θ, under the model specified in the PRED (PREDPP) subroutine. Random variables η and ε (if any) have no effect on the predictions and may be omitted. If the only purpose of the run is to obtain simulated values, and these variables are present, it is best (but not required) that their variances be fixed to 0. NONMEM does not compute the objective function in this circumstance, which has certain advantages.

NONMEM can also perform a Simulation Step, in which another type of simulation is performed. In the Simulation Step, each value of the DV data item of each record with MDV=0 is replaced by a simulated observation generated from the model, but including statistical variability†. The PRED (PREDPP) routine uses η and ε values that are supplied by NONMEM according to user-specified random distributions (e.g., with variances given by the initial estimates of Ω and Σ). If Ω and Σ matrices are fixed to zero, for example, the simulated values are the same as the

† During the Simulation Step, values of F computed by PRED or PREDPP for records having MDV=1 are irrelevant and are ignored by NONMEM.

predictions described above.

If the data are then displayed by the Table Step, the DV column for records with MDV=0 contains the simulated observations obtained from the Simulation Step. For records having MDV=1, the DV column contains whatever was in the original data record. The PRED column of the table contains predictions as described above. If the Estimation Step was not implemented, the values of θ used for these predictions are the initial values. If the Estimation Step was implemented, the values of θ used for the predictions in the PRED column are the final parameter estimates. Note that the observations that are fit during the search are the simulated values obtained by the Simulation Step.

Often data are simulated using the Simulation Step, then analyzed using one or more other steps (e.g. Estimation and Covariance Steps), and this process is repeated a fixed number of times, using the same model. The Simulation Step accommodates this easily with the notion of a NONMEM subproblem, whereby these steps are repeated within the same NONMEM problem. However, on occasion it can be useful to have multiple problems (see Section 4.7), where one problem implements the Simulation Step, and the subsequent problem implements other steps. For example, this is one way to obtain different initial parameter estimates for the Estimation Step than for the Simulation Step.

The `ONLYSIMULATION` option causes NONMEM to suppress evaluation of the objective function. With this option, PRED-defined variables displayed in tables and scatterplots (see Section 4.13) are simulated values, i.e., use simulated ηs and initial θs, and weighted residual values in tables and scatterplots are always 0.

References: Users Guide IV (NM-TRAN) III.B.13
References: Users Guide VI (PREDPP) III.E.2, L.1 , IV.B.1-2, C, G.1

4.8.1. More About $SIMULATION

With simulation, subroutines SIMETA and SIMEPS are used.

With simulation and subproblems, the data set for each subproblem after the first is the same data set used by the previous subproblem, and includes any changes (transgeneration) made by the previous subproblem. The following NONMEM reserved variables are of interest:
IREP, NREP

NONMEM subroutine RANDOM may be used in abbreviated code to obtain numbers from a random source (nmiv, nm7).

The $SIMULATION record has other options, including:

a random seed and options `NEW`, `NORMAL`, `UNIFORM`, or `PARAMETRIC` for each of several random sources;
`TRUE=INITIAL`, `TRUE=FINAL`, or `TRUE=PRIOR`, to specify what the "true parameter values" for the Simulation should be;
`PREDICTION` or `NOPREDICTION` to specify whether the Y (or F) variable or the DV variable is set to the prediction;
`REQUESTFIRST` or `REQUESTSECOND` to specify if any eta partials are to be computed.

NONMEM can use the BOOTSTRAP method for simulations. With BOOTSTRAP, other options are possible:

`REPLACE` or `NOREPLACE`
`STRAT` or `STRATF`.

4.9. Files for Subsequent Processing: the $TABLE Record

NONMEM can write the data for a table to an external formatted file, as requested by the FILE option of the $TABLE record. Other computer programs can read these files. Such programs can perform further analysis or provide improved graphical displays. These files normally contain header lines similar to those in a printed table, but the header lines can be suppressed entirely or in part by means of the `NOHEADER` or `ONEHEADER` options, respectively.

Tables may be written to the same or to different table files.

References: Users Guide IV (NM-TRAN) III.B.16

4.9.1. More about $TABLE and $SCATTER

With the $TABLE record, `NOHEADER` are `NOTITLE` (suppresses the table titles) and `NOLABEL` (supresses column labels) may be used.

Some options may be used only with a table file.

Options `NOFORWARD` and `FORWARD` control whether a table file which is used with multiple problems is positioned at the start of the file or forwarded to the end of the file.

Option `NOPRINT` may be used suppress the table in the NONMEM report, or `PRINT` to include it as ususal. A printed table is limited to 8 items but a non-printed table file may have an ulimited number of items (controlled by PDT in $SIZES with default 500).

`FORMAT` supplies an alternate format for every numeric item in a table file (the default is s1PE11.4). An alternate name for this option is `DELIM`.
`RFORMAT` supplies an alternate format for the full numeric record of a file.
`LFORMAT` supplies an alternate format for the full label record in a file.

Other options can be used with both printed tables and table files.

`FIRSTONLY` (include only the first data record from each individual record)
`BY` (sort records in the table)
`NOAPPEND` (suppress items DV, PRED, RES, WRES)
`APPEND` (list items DV, PRED, RES, WRES; this is the default)

With a $SCATTER record, additional options are:

`FIRSTONLY` (include only the first data record from each individual record)
BSTONLY (include only the observation records, having MDV=0)

The option `ABS0` is similar to `ORD0` described in Chapter 9, but adds a line zero line on the abscissa axis of the scatterplots.

Many additional diagnostic and reserved variables may be listed in tables and scatters; see 6.3 below.

With the Monte-Carlo generated diagnostics, new options of the $TABLE record may be used. Note that if these options affect the values of the weighted residual, the scatterplots will also be affected.

```
ESAMPLE=n1
WRESCHOL
SEED=n2
RANMETHOD=[n|S|m]
```

4.10. Data Checkout Mode

NONMEM's data checkout mode is intended for preliminary display of data without the use of a model. In data checkout mode, the PRED routine is not called. Predictions, the objective

function, residuals, and weighted residuals are not computed. Only the Table and Scatterplot Steps can be implemented in the problem. With NM-TRAN, this mode is requested by coding the option `CHECKOUT` on the $DATA record. A $SUBROUTINES record and abbreviated code are required, but they have no effect and need only be syntactically correct.

References: Users Guide IV (NM-TRAN) III.B.6

4.11. Obtaining Individual Parameter Estimates - Conditional Estimates of ηs

With population data, NONMEM can obtain estimates of individual-specific true values of η from any given set of values of θ, Ω, Σ, and the individual's data. These are called conditional estimates of η. When the conditional estimates are obtained after estimation is carried out by the First-Order method, they are referred to as "posthoc" estimates. With NM-TRAN, they are requested by the option `POSTHOC` on the $ESTIMATION record.

References: Users Guide IV (NM-TRAN) III.B.14

4.12. Population Conditional Estimation Methods

NONMEM can obtain conditional estimates of η variables as part of the computation of population parameter estimates. These are called conditional estimation methods. With NM-TRAN, such methods are requested by including the option `METHOD=CONDITIONAL` (or `METHOD=1`) on the $ESTIMATION record. (The option `METHOD=ZERO`, or `METHOD=0`, requests the conventional First-Order method and is the default.) There are two conditional estimation methods. If NONMEM uses only first-order approximations, this is the First-Order Conditional Estimation Method. This has one variation, interaction, which takes into account η-*eps* interaction and is requested by the additional option `INTERACTION` on the $ESTIMATION record. If NONMEM uses a certain second-order approximation, this is the Laplacian method, which is requested by the additional option `LAPLACIAN` on the $ESTIMATION record. Interaction may be specified with any method, including the Laplacian method.

Note that this usage of the term CONDITIONAL is different from the usage on the $SCATTERPLOT, $TABLE, and $COVARIANCE records, in which it refers to the circumstances under which the step in question is implemented.

Option `CENTERING` requests that the average conditional estimates of each eta be constrained to be close to 0.

References: Users Guide IV (NM-TRAN) III.B.14

4.13. Displaying PRED-Defined Variables and Conditional Estimates of ηs

NONMEM can display PRED-defined variables in table and scatterplots. With NM-TRAN, any variable appearing on the left-hand side of an assignment statement in abbreviated code can be displayed by listing it in a $TABLE or $SCATTER record. If the data are population, NONMEM can also display conditional estimates of η. With NM-TRAN, variables ETA(1), ETA(2), etc., can be simply listed in $TABLE and $SCATTER records. When conditional estimation is not performed, the values displayed are zero. Displayed values of PRED-defined random variables will use conditional estimates of η if they have been obtained, otherwise they will be typical values. This feature is available with PREDPP, as well as with user-written PRED routines. For example, the following records could replace the $ESTIMATION record in Figure 12.2:

```
$ESTIMATION POSTHOC
$TABLE ETA(1) EMAX
```

The $ABBREVIATED record can be used to limit the number of variables available for display when the number is excessive.

References: Guide III (Installation) V.2.4
References: Guide IV (NM-TRAN) III.B.16-17
References: Guide VI (PREDPP) III.J, IV.E

4.14. Mixture Models

A mixture model is a model that explicitly assumes that the population consists of two or more sub-populations, each having its own model. For example, with two sub-populations, one might assume that some fraction p of the population has one set of typical values of the PK parameters, and the remaining fraction 1-p has another set of typical values. Both sets of typical values and the mixing fraction p may be estimated. For each individual, NONMEM also computes an estimate of the number of the subpopulation of which the individual is a member. The user must supply a FORTRAN subroutine called MIX or a $MIX block of abbreviated code to compute the fractions p and 1-p.

Reserved variables NSPOP, P, MIXNUM, MIXEST, MIXP and MIXPT can be used in abbreviated code. Reserved variable TEMPLT may be used.

References: Users Guide VI (PREDPP) III.L.2

4.15. PRED Error Return Codes and Error Messages in File PRDERR

A PRED routine can return a PRED error return code (1 or 2) to NONMEM, indicating that it is unable to compute a prediction for a given data record with the current values of θ's and η's. For example, PREDPP returns error return code 1 when a basic or additional PK parameter has a value that is physically impossible (e.g., a scale parameter which is zero or negative). Error return codes can also be specified by the user in user-written code or in abbreviated code using the EXIT statement. One reason for doing this is to constrain parameters in order to avoid floating point machine interrupts. The PRED error recovery option determines what action NONMEM will take. With NM-TRAN, the PRED error recovery option is either `ABORT` (which is the default) or `NOABORT`, and is specified on the $ESTIMATION and $THETA records.

If an error return code is returned during the Simulation, Covariance, Table or Scatterplot Step, or during computation of the initial value of the objective function, NONMEM will abort. If the error return code is returned during the Estimation or Initial Estimates Step, NONMEM will try to avoid those values of θ and η for which the error occurs. If they cannot be avoided, NONMEM's actions depend on the error return code value, as follows:

1 If `NOABORT` is specified on $ESTIM or $THETA, try to avoid the current values of θ and η. If `ABORT` is specified on $ESTIM or $THETA, then abort.

2 Abort in all cases.

`NOABORTFIRST` may be specified on $THETA (nmvi) Same as NOABORT option, but also applies to the first value of the theta vector that is tried.

`NOHABORT` may be specified on $ESTIM (nm7).

PRED routines may optionally provide text accompanying the error return code. NONMEM writes all text associated with error return codes to a file, PRDERR. The contents of this file should always be carefully reviewed.

References: Users Guide III (Installation) III.2.1.1
References: Users Guide IV (NM-TRAN) IV.A, IV.C.5-6
References: Users Guide VI (PREDPP) III.K, IV.F

4.16. User-Written Subroutines

Although most NONMEM applications can be accomplished using NM-TRAN abbreviated code, there are cases in which user-written FORTRAN subroutines are needed. The `$SUBROUTINES` record allows the user to specify the names of user-written routines that are needed in the NONMEM load module. A user may choose to write his own PRED, PK, ERROR, MODEL, DES, or AES subroutine. Some subroutines that are distributed with NONMEM are dummy, or "stub" routines, that do nothing. Of these, subroutines CCONTR, CONPAR, CONTR, and CRIT
ARE THESE STILL OK? AJB 7/3/2013
OTHER STUBS TOO: prior THETAI THETAR
can be replaced to obtain an objective function different from the default. NONMEM subroutine MIX must be replaced for mixture models. PREDPP subroutine INFN may be replaced by user-written code. The names of all such routines are specified using the identically named options of the `$SUBROUTINES` record, e.g., `PRED=subname`, `CONTR=subname`, etc. User-written routines may call other FORTRAN subroutines, which can be specified for inclusion in the load module using the option `OTHER=subname`.

With user-written CONTR routines, the NM-TRAN $CONTR record may be useful.

References: Users Guide IV (NM-TRAN) III.B.4, B.6

4.17. PRIOR

The PRIOR subroutine and $PRIOR record allows a Bayesian penalty function to be added to the NONMEM objective function. This serves as a constraint on the estimates of THETA, OMEGA, and SIGMA and thus as a way for stable estimates to be obtained with insufficient data.

NONMEM subroutines that may be used are NWPRI and TNPRI (nmvi). With NWPRI, informatively-named $THETAP, $OMEGAP, $SIGMAP records can be used to provide prior information (nm73).

The option NOPRIOR of the $ESTIMATION record controls whether or not the prior information is used for a given Estimation Step.

References: Introduction to NONMEM Version VI

5. Observations of Two Different Types

An NM-TRAN control stream is shown in Figure 12.3, for the analysis of a data set which contains observations of two different types. A fragment of the data set, shown in Figure 12.4, contains the data for one individual. This example illustrates how concentration and effect data can be fit simultaneously, and includes many of the advanced features described in this chapter, such as pharmacodynamic modeling in the $ERROR statements, correlation between elements of Σ, and the L2 data item.

Suppose that the data set for the phenobarbital example of Chapter 2 is modified to include both concentration and effect observations, and that a data item called TYPE is used to distinguish between them. When TYPE is 1, DV contains an effect measurement. When TYPE is 2, DV contains a concentration. The $PK statements are the same as those of Figure 2.12. The $ERROR statements are the same as those of Figure 12.1, except that the elements of θ and η are renumbered to follow those used in the $PK statements. The (random) variable Y1 is assigned the same value as Y in the $ERROR statements of Figure 12.1 The (random) variable Y2 is assigned the same value as Y in the $ERROR statements of Figure 2.12, except that ε_2 is used rather than ε_1.

The input data file contains observations of both types which were made at the same time value. The event records therefore include the L2 data item. Figure 12.4, like Figure 2.7, shows the data for the first individual, but includes TYPE and L2 data items and effect observations. Note that the L2 data item has a different value for each multivariate observation within the individual record. (The values 1 and 2 are chosen arbitrarily and may be re-used for the L2 data items in the next individual's data, if desired.)

The $THETA, $OMEGA, and $SIGMA records contain the values shown in Figures 2.12 and 12.1 and one other value, 2.8, for the covariance $\Sigma_{12} = cov(\varepsilon_1, \varepsilon_2)$. The estimate 2.8 is chosen so that the correlation is, arbitrarily, .5 ($2.8 = \Sigma_{12} = (\Sigma_{11}\Sigma_{22})^{\frac{1}{2}}\ corr = (8 \times 4)^{\frac{1}{2}}\ .5$).

```
$PROBLEM COMBINED PK/PD MODEL
$INPUT   ID TIME AMT WT APGR DV TYPE L2
$DATA    COMBDATA
$SUBROUTINE ADVAN1
$PK
   TVCL=THETA(1)+THETA(3)*WT
   CL=TVCL+ETA(1)
   TVVD=THETA(2)+THETA(4)*WT
   V=TVVD+ETA(2)
                       ; THE FOLLOWING ARE REQUIRED BY PREDPP
   K=CL/V
   S1=V
$ERROR
 EMAX=THETA(5)+ETA(3)
 C50=THETA(6)+ETA(4)
 E=EMAX*F/(C50+F)
 Y1=E+ERR(1)
 Y2=F+ERR(2)
 Q=1
 IF (TYPE.EQ.2) Q=0
 Y=Q*Y1+(1-Q)*Y2
$THETA  (0,.0027) (0,.70) .0018 .5 100 20
$OMEGA  .000007 .3 400 16
$SIGMA BLOCK(2) 4 2.8 8
$ESTIMATION
```

Figure 12.3. The input to NONMEM-PREDPP for analysis of the population phenobarbital data, including both concentration and effect observations.

```
1    0.    25.0    1.4      7      .   2   0
1    2.0      .    1.4      7    6.0   1   1
1    2.0      .    1.4      7   17.3   2   1
1   12.5    3.5    1.4      7      .   2   0
1   24.5    3.5    1.4      7      .   2   1
1   37.0    3.5    1.4      7      .   2   0
1   48.0    3.5    1.4      7      .   2   1
1   60.5    3.5    1.4      7      .   2   0
1   72.5    3.5    1.4      7      .   2   1
1   85.3    3.5    1.4      7      .   2   0
1   96.5    3.5    1.4      7      .   2   1
1  108.5    3.5    1.4      7      .   2   0
1  112.5      .    1.4      7    8.0   1   2
1  112.5      .    1.4      7   31.0   2   2
```

Figure 12.4. The first individual's phenobarbital data, including both concentration and effect observations.

The above $ERROR statements can be coded more simply.

```
$ERROR
 EMAX=THETA(5)+ETA(3)
 C50=THETA(6)+ETA(4)
 E=EMAX*F/(C50+F)
 IF (TYPE.EQ.2) THEN
 Y=F+ERR(2)
 ELSE
 Y=E+ERR(1)
```

```
      ENDIF
```
Figure 12.5. Alternate $ERROR statements

6. Supplemental List of Features through NONMEM 7.3

With NONMEM 7 there are many new features, including new Estimation Methods. This section lists features of NONMEM, PREDPP, and NM-TRAN that are not discussed elsewhere in this guide. The version of NONMEM in which each feature appears is listed. The user should consult other guides for details.

6.1. NONMEM Features

Odd-Type Data (nmv)

Non-continuous observed responses ("odd-type data") can be analyzed. $ESTIMATION options LIKELIHOOD or -2LL must be used. Y is set to a (conditional) likelihood.
Reserved variable F_FLAG may be used (nmvi).

New methods of Estimation

METHOD=HYBRID with option ZERO (nmv)
STIELTJES with options GRID, REPEAT1, REPEAT2, ZERO (nmvi)
ITS Iterative Two Stage (nm7)
Expectation-Maximization (EM) and Monte Carlo Bayesian (nm7)

Expectation feature (nmv)

This feature uses the NONMEM marginal (MRG_) data item. MRG_ identifies records for which NONMEM computes and displays marginal quantities (expectations) Expectations are computed when ICALL=5.

Raw data average feature (nmv)

This feature uses the NONMEM raw-data (RAW_) data item. RAW_ identifies template records for which NONMEM computes and displays raw-data averages. Raw data averages are computed when ICALL=6. Reserved variables TEMPLT and the $OMIT record may be used (nmvi). The NONMEM utility routine RANDOM may be used to obtain numbers from different random sources.

Non-parametric analysis methods (nmvi)

The $NONPARAMETRIC record is used to request the Non-parametric method of analysis. Options include:
MARGINALS or ETAS, MSFO=filename, RECOMPUTE, EXPAND, NPSUPP=n or NPSUPPE=n

SORT option of $ESTIMATION (nmvi)

With classical methods, individual contribution to the objective function and gradients may be sorted before they are summed, so that smaller numbers are summed before larger numbers.

Reserved Variables YLO/YUP (nmvi)

During the analysis an interval is defined in which (or outside of which) an observation is conditioned to exist. Reserved variable PR_Y is also of interest.

Reserved Variables CTLO/CTUP (nmvi)

An observation may be the event that the value of a normally distributed variable falls in a given interval. Reserved variable PR_CT is also of interest.

NONMEM Repetition feature (nmvi)

This features uses reserved variables RPTI,RPTO,RPTON,PRDFL. An alternate way is to use the RPT_ data item.
QUESTION TO BOB: Are these two different features?

MU Modeling (MU Referencing) (nm7)

MU_i variables may be used in Abbreviated code with EM methods of Estimation. NM-TRAN checks the use of MU_i variables, unless option *NOCHECKMU* of the $ABBR record is used (nm73). Thetas may be input and reported in their natural domain, even when used as logs (e.g., linear MU referencing) using $THETAI and $THETAR records (nm73).

New method of setting initial values of thetas, omegas, and sigmas. (nm72)

See CHAIN option of $ESTIMATION and $CHAIN.

Multiple Estimation steps (nm72)

If the $ESTIMATION record is present more than once within a problem, then each subsquent record requests a separate Estimation Step rather than providing more options for a single Estimation Step.

BOOTSTRAP method (nm73)

BOOTSTRAP may be specified with $NONPARAMETRIC and $SIMULATION records. This requests that a bootstrap sample be used. Options STRAT and STRATF may be used for stratification. With $SIMULATION, options REPLACE or NOREPLACE may be used.

More than 2 levels of mixed effects (nm73)

Increased number of mixed effects levels. Random effects across groups of individuals, such as clinical site, can be modeled. The $LEVEL record is used.

Alternate method (TYPE2) for single-subject analysis (nm73)

All the subjects may be analyzed together, but with $OMEGA diagonal values fixed to a special value 1.0E+06.

New values of MDV (nm73)

MDV may be set to 100, 101. Such records are ignored during Estimation. Reserved variables MDVI1, MDVI2, MDVI3 may also be used; they are defined in include file nonmem_reserved_general.

Initial Estimates for ETAs feature (nm73)

By default, the initial value used for ETA's in the Estimation Step search is 0. The $ETAS and $PHIS records provide user-supplied initial estimates.

Tranformations of THETA values (nm73)

$THETAI transforms the initial values in the $THETA and $THETAP records. $THETAR transforms the final theta values for the NONMEM report and additional output files. May be used with MU Modeling.

Constraints on model parameters (nm73)

Additional algorithmic constraints may be imposed upon model parameters by use of the subroutine CONSTRAINT. Option CONSTRAIN of the $ESTIMATION record and the $ANNEAL record may be used to give information to the subroutine. This feature is available only for the EM and Bayesian algorithms.

6.2. Miscellaneous Features

Interactive control of NONMEM (nm7)

A NONMEM run can now be controlled to some extent from the console by issuing certain control characters.

Dynamic Memory Allocation (nm72)

No need to recompile NONMEM or NM-TRAN for large problems. Most arrays are sized automatically. If necessary, the $SIZES record may be used. E.g., the default maximum number of data items per data record is 50, but may be increased by specifying a larger value for PD.

Parallel Computing (nm72)

Parallel Computing is requested using the nmfe option -parafile and specified using .pnm files. The options PARAFILE of the $ESTIMATION and $COVARIANCE records may also be used.

6.3. Changes to NONMEM Outputs

Reports include Covariance and Correlation Matrices for OMEGA and SIGMA (nm72)

Reports include ETABAR, SE, N, P VAL (nm7)

Option ETABARCHECK of the $ESTIMATION record may be used.

Reports include ETAshrink, EBVshrink, EPSshrink (nm7)

Eta shrinkage evaluation using empirical Bayes variances (EBVs, or conditional mean variances) is reported. The ETASTYPE option of the $ESTIMATION record and the ETASXI reserved variable in abbreviated code may be used to control which etas from which subjects are included.

Reports include tag labels: #METH etc. (nm7)

Raw and additional output files: root.ext, root.cov, root.xml, etc. (nm7)

These files provide numerical results in a columnar format. $ESTIMATION record option ORDER may be used to control the order of theta, omega, sigma in these files. $ESTIMATION record option NUMDER may be used to request files with numerical and analytic eta derivatives: root.fgh, root.agh (nm73)

Tables and Scatters may request NONMEM-generated items

Elements of G and H (e.g., G11, H11) and elements of ETA (nmvi)

A range of etas using the format ETAS(x:y) may be requested (nm73).

OBJI (Objective function values for each individual) (nm72)

Additional statistical diagnostic items (nm7, nm73)

In addition to the PRED, RES, and WRES items, the following may be listed.

`PREDI`, `RESI`, `WRESI`
`CPRED`, `CRES`, `CWRES`
`CPREDI`, `CRESI`, `CWRESI`
`CIPRED`, `CIRES`,`CIWRES`
`CIPREDI`, `CIRESI`,`CIWRESI`
`NIPRED`, `NIRES`, `NIWRES`
`IPREDI`, `IRESI`,`IWRESI`
`IPRD`, `IRS`,`IWRS`
`EPRED`, `ERES`, `EWRES`

Monte-Carlo generated diagnostics and are not linearized approximations like the other diagnostic types. These include

`ECWRES`
`EIPRED`, `EIRES`,`EIWRES`
`NPDE` Monte-Carlo generated normalized probability distribution error) (nm71)
`NPD` correlated value of NPDE (nm72)

A reserved variable of interest when evaluating residuals and weighted residuals is MDVRES which may be set in PRED to cause NONMEM to treat an observation as missing.

6.4. PREDPP

New PREDPP data items in $INPUT: XVID1 XVID2 XVID3 XVID4 XVID5 (nm72)
: Special values of EVID allow repeated observation records, e.g., for Stochastic differential equations.

CMT and PCMT values 100,1000
: Specification of the default compartment for output (nm, nm73)

Compartment Amounts A(i), TSTATE (nmvi)

A_0 (compartment initialization) (nmvi)
: May be used with any ADVAN. A_0FLG

I_SS (Initial Steady State) for general non-linear models (nmvi)
: It is possible to specify initial conditions for the differential equations using the I_SS (Initial Steady State) feature. Reserved variable ISSMOD may be used.

DES array: COMPACT vs. FULL for general non-linear models (nmv)

ISFINL reserved variable with AES and DES (nmvi)
: Allows the abbreviated code to take special action on the final call to AES and DES for an integration interval.

6.5. NM-TRAN

6.5.1. General Features

Case-insensitivity (nm72)
: Both lower and upper case may be used in the NM-TRAN control file.

Continuation and line length (nm73)
: Any line may be continued with "&" and may be 67000 characters long.

Warning messages (nmv)
: The numbers of warning messages of various types may be controlled using the $WARNING record.

6.5.2. Data Preprocessor

$DATA TRANSLATE (nmv, nm73)
: Allows TIME and II values to be rescaled, with specified number of decimal points.

ill-formed data files (nmvi)
: NM-TRAN is better able to handle a data file whose final line does not terminate correctly.

tabs in data files (nmvi)
: NM-TRAN can read data files in which tabs are present, and whose lines end with ^M.

$DATA BLANKOK (nmvi)
: NM-TRAN will not allow blank lines in a data file unless the BLANKOK option is used.

Larger data files (nmvi)
: The RECORDS=n option of $DATA may specify a number as large as 99999999.

6.5.3. Abbreviated Code

Fortran 90/95 syntax may be used.
: For example, logical expressions may be written using symbols ==,>, instead of .EQ., .GT., etc.

Increased number of THETA, ETA, EPS (nm72)
: Subscripts of THETA, ETA, EPS may be as large as 999.

$ABBR record: COMRES, COMSAV
: Creates variables that are saved between nonmem passes. NONMEM Reserved variables COM, COMACT are used.

$ABBR record: DERIV2 (nmIV), NOFASTDER(nm72)
: Affects generated code in FSUBS.

$ABBR REPLACE (nm73)
: Any character string may be replaced. This allows for symbolic reference to thetas, etas, and epsilons. Replacement with selection by data item and parameter is permitted.

$ABBR DECLARE (nm73)
: Allows integer variables and array (subscripted) variables to be used in Abbreviated code.

Recursive abbreviated code (nmvi)
: Allows a random variable to retain the value from the previous data record instead of being set to zero. May be used to implement recursive kinetics in $PRED.

User-written functions FUNCA, ..., FUNCI and VECTRA,VECTRB,VECTRC (nmvi)
: The user may supply functions. They may have scalar or vector-valued arguments. When they are used in abbreviated code, the eta derivatives of the arguments are computed correctly. With nm73, the number of functions increases from 3 to 9.

Functions PHI, INT, MOD, MIN, MAX, GAMLN (nm7)
: Additional built-in functions are permitted. INT, MIN, MOD, MAX are Fortran functions. PHI gives the value of the cumulative distribution function. GAMLN gives an accurate evaluation of the logarithm of the gamma function.

WRITE/PRINT statements
: Character strings, format specification, Array options FULL vs. DIAG

DO WHILE, DO WHILE(DATA) statements
: Looping; transgeneration.

Include files for NONMEM_RESERVED variables (nm73)
: If the name of an include file starts with NONMEM_RESERVED, it may contain definitions of variables that will be parsed by NM_TRAN for use in abbreviated code.

6.5.4. Reserved Variables in Abbreviated Code

Here is a partial list of reserved variables that are not mentioned elsewhere in this guide.

ICALL
: NONMEM reserved variable. Tells PRED when NONMEM is doing Run initialization, Problem initialization, Estimation, Problem finalization, Simulation, Expectiation, Data Average. (nmv)

NEWIND
: NONMEM reserved variable. Tells PRED when data from a new individual record is starting.

NIREC, NDREC (nmvi)
: NONMEM reserved variables. Input data file record counters.

LIREC NINDR INDR1 INDR2 reserved variables (nmvi2.0)
: NONMEM reserved variables. Descriptive of the individual record.

MSEC, MFIRST, IFIRSTEM
: NONMEM reserved variables. Tells PRED which derivatives to compute.

OMEGA, SIGMA, SETHET, SEOMEG, SESIGM (nmvi)
: NONMEM reserved variables. The current values of OMEGA, SIGMA, et. al., may be used in abbreviated code.

IIDX,CNTID (nmvi)
: NONMEM reserved variables. Individual contribution to the objective function.

PRED_,RES_,WRES_, and other variables
: Variables with similar names and the same values as statistical diagnostic items PRED_, RES_, WRES_, CPRED_, CRES__, CWRES, etc., may be used on the right in $PRED and $ERROR blocks (nm7)

NONMEM_reserved_general (nm73)
: This is a file in the util directory with declarations for many additional resrved variables.

6.6. Utility Routines

This is a list of utility programs found in the util directory.

nmfe73
: The nmfe shell script has many new options, including options for parallel computing.

finedata
: Augments an NM-TRAN data file to incorporate additional, non-observation, time values spaced at regular increments.

nmtemplate
: Performs variable substitution on appropriately tagged control stream template files, and produces new control stream files. Compare with the $ABBR REPLACE feature, above.

table_compare
: Compares the numerical values between two table files produced by the $TABLE record.

table_to_xml
: Converts additional output table files produced by NONMEM to XML Formatted files.

xml_compare
: Compares the contents of two NONMEM report XML files.

6.7. Other Options

Other Options for Estimation (All methods)
: FNLETA (Affects how final ETA's are obtained)
ETADER (For evaluating individual variances by numerical derivative methods.)
MCETA (Affects MAP (Mode A Posteriori) eta optimization)
NUMDER (Asks NONMEM to generate files with numerical and analytic eta derivatives)
NUMERICAL (Affects second derivatives for Laplacian method)
OPTMAP (Affects Optimization Method to find Eta values)
SORT (sort objective function values for each individual before they are summed) (nmvi)

Other Options for Estimation (Classical methods)
: THETABOUNDTEST, OMEGABOUNDTEST,SIGMABOUNDTEST (Affects error messages from NONMEM.)
NONINFETA (Useful when some etas are not used with some individual's data)

Other Options for Expectation-Maximization (EM) and Monte Carlo Methods (nm7)
: AUTO
BAYES
CINTERVAL

CITER/CNSAMP
CTYPE
DF
DIRECT,
EONLY
GRD
IACCEPT OACCEPT PACCEPT
IMPMAP,
ISAMPEND, ISAMPLE, ISAMPLE_ variables
ISCALE_MIN, ISCALE_MAX
ITS
MAP,
MAPINTER
MAPITER
NBURN
NITER/NSAMPLE
OSAMPLE_ variables
PSAMPLE_ variables
PSCALE_ variables
RANMETHOD
SAEM,
SEED

References: Introduction to NONMEM 73