NONMEM VI
New Features

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General Improvements

- All Version V known bugs are fixed
- New warning messages
- Stability and speed improved for conditional estimation methods

Stability – FOCE with INTERACTION – starting with 6 different initial estimates

Version V			Version VI beta		
Term.	Covr.	OFV	Term.	Covr.	OFV
ok	ok	-22190.891	ok	ok	-22190.892
E134, 1.4		-19987.462	ok	S	-22190.892
E136		-20796.963	ok	ok	-22190.892
E134, 2.7		-22185.224	ok	ok	-22190.892
ok	ok	-22189.452	ok	ok	-22190.892
ok	ok	-22190.891	ok	ok	-22188.795

Stability – FOCE with INTERACTION – starting with 6 different initial estimates

Version V			Version VI beta		
Term.	Covr.	OFV	Term.	Covr.	OFV
E136		-22405.336	ok	S	-22405.348
E136		-19491.130	ok	ok	-22405.347
E134, 1.9		-20729.658	E134, 2.9		-22405.347
ok	S	-22405.116	E134, 2.9		-22405.290
E134, 1.5		-19814.708	ok	ok	-22405.347
E134, 0.4		-19859.672	E134, 2.9		-22405.347

NONMEM-related Features

- Interaction option now available for FO, Laplacian, and Hybrid.
- New option for $ESTIM, ETABARCHECK

  1) Complete an analysis and generate an msf file as usual.

  2) With ETABARCHECK included on $ESTIM
  Simulate using the results of 1) and estimate.

  3) P-values output with results of 2 related to the probability that ETABAR from 2) is different from ETABAR from 1).

  Can be used with Mixture models.

NONMEM-related Features

- Easier simultaneous analysis of continuous and odd-type data. F_FLAG variable.
- Frequency Prior for data-analytic purposes or to simulate parameter values. Two utilities, NWPRI (user specified prior) and TNPRI (prior directly from a previous NONMEM analysis via an msf file).
- YLO,YUP. Observation is conditioned to be inside or outside a one- or two-sided interval, e.g. YLO=BQL.
- Repeat feature. Can pass a sequence of data records repeatedly. Nesting is possible. Kinetics can be computed using a convolution integral.

NONMEM-related Features

- Maximum number of submodels for a mixture model can be specified in SIZES
- New option on $SIMUL when an msf file is input. TRUE, e.g. TRUE=FINAL or TRUE=INITL (default). Default is different from NONMEM V behavior.
- Population parameter values produced using a frequency prior are stored in a Common.

PREDPP-related Features

- Model event times, MTIME( ). PK parameters defined in $PK block. MTIME( ) is a time to which the system is advanced. When TIME=MTIME( ) then indicator variables are set/reset. These variables can be used to change some aspect of the system such as a rate of infusion or a term in a diff. eq.
- Compartment amounts can be initialized in $PK

NM-TRAN-related Features

- Expanded use of the IGNORE option on $DATA, e.g. IGNORE=(WT.GT.100)
- New ACCEPT option on $DATA, e.g. ACCEPT=(WT.LE.100)
- DO WHILE (DATA) automatically and transparently manages the calls to PASS in an initialization/finalization block
- TAN, ASIN, ACOS, ATAN recognized by NM-TRAN
- Utility routine RANDOM can be used in initialization/finalization blocks
- Support for recursive definition of random variables

Recursive code in $PRED for multiple dosing

```
K=THETA(1)*EXP(ETA(1))
IF (TIME.EQ.0) THEN
   A=AMT
   T=TIME
ELSE
   A=A*EXP(-K*(TIME-T))+AMT
ENDIF
T=TIME
```

NM-TRAN-related Features

- User-written Functions, FUNCA, FUNCB, FUNCC (Abbreviated Functions). The function can be dependent on a random variables. A vector may be defined in abbreviated code, VECTRA(n), VECTRB(n), VECTRC(n) and then used as an argument to an abbreviated function, e.g. FUNCA(VECTRA). The function itself must be coded in Fortran.

NM-TRAN-related Features

- Value of RECORDS option on $DATA may be a label, e.g. RECORDS=ID. First problem with this option will read all records until the ID changes, i.e. the first individual. Second problem with $DATA and this option along with NOREWIND will read all records for the second individual, etc.
- The INCLUDE record may now have an integer follow the filename, e.g. INCLUDE ctlfile2 11. The ctlfile2 file will be included 11 times in the control stream.

Independent Estimation of Individual Data – Control stream to analyze 129 subjects individually.

```
$PROB RUN# xxx
$INPUT C ID STUY SUBJ EVID RATE=DROP AMT ADDL II TIME
   DV LOGC MDV
$DATA xxx.csv RECS=ID
$SUBROUTINES ADVAN4 TRANS4
```

- $PK
- KA=THETA(1)
- CL=THETA(2)
- V2=THETA(3)
- Q=THETA(4)
- V3=THETA(5)
- ALAG1=THETA(6)
- S2=V2/1000
-
- $ERROR
- Y=F + F*ERR(1)

Independent Estimation of Individual Data

```
$THETA
(.1, 1.97, 10)          ;[KA]
(25, 516, 3000)         ;[CL]
(50, 625, 3000)         ;[V2]
(1, 40, 500)            ;[Q]
(100, 900,20000)        ;[V3]
(0, 0.336, 1.2)         ;[ALAG1]

$OMEGA
  0.05                  ;[P]

$EST METHOD=0 MAXEVAL=9999 PRINT=0 NOABORT SIGDIGITS=4
$COVARIANCE SPECIAL PRINT=E
$TABLE ID SUBJ TIME NOPRINT ONEHEADER FILE=xxx.tab

INCLUDE xxx2.txt 128
```

Independent Estimation of Individual Data

```
$PROB RUN# xxx2
$INPUT C ID STUY SUBJ EVID RATE=DROP AMT ADDL II TIME DV
   LOGC MDV
$DATA xxx.csv RECS=ID NOREWIND
$THETA
(.1, 1.97, 10)       ;[KA]
(25, 516, 3000)    ;[CL]
(50, 625, 3000)    ;[V2]
(1, 40, 500)         ;[Q]
(100, 900,20000) ;[V3]
(0, 0.336, 1.2)     ;[ALAG1]
$OMEGA
  0.05 ;[P] PROPORTIONAL COMPONENT
$EST METHOD=0 MAXEVAL=9999 PRINT=0 NOABORT SIGDIGITS=4
$COVARIANCE SPECIAL PRINT=E
$TABLE ID SUBJ TIME NOPRINT NOHEADER FORWARD FILE=xxx.tab
```

NM-TRAN-related Features

- Compartment amounts, A(n), can be used as right-hand side quantities in $PK. The time at which A(n) are computed is stored in TSTATE. ($OMEGA or $MSFI record must precede the $PK record and include the option POP=m, the number of population ETA variables.
- The code for an INFN subroutine can be provided using a $INFN record.

NM-TRAN-related Features

- Variables defined in copying blocks of abbreviated code are now implicitly saved in NMPRD4.

  IF(COMACT.EQ. ...) THEN

  T1/2=0.693*V/CL

  ENDIF

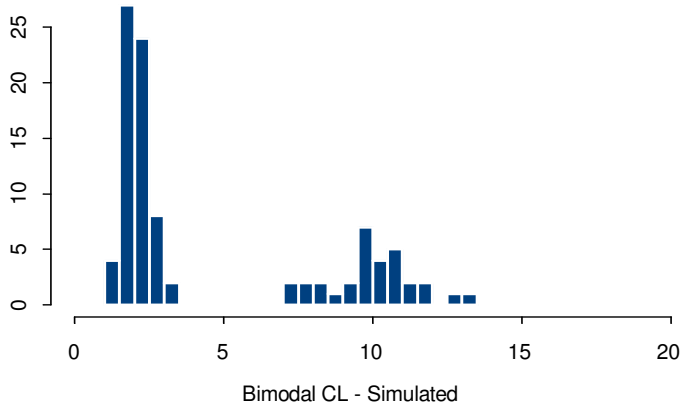
  T1/2 saved in NMPRD4.

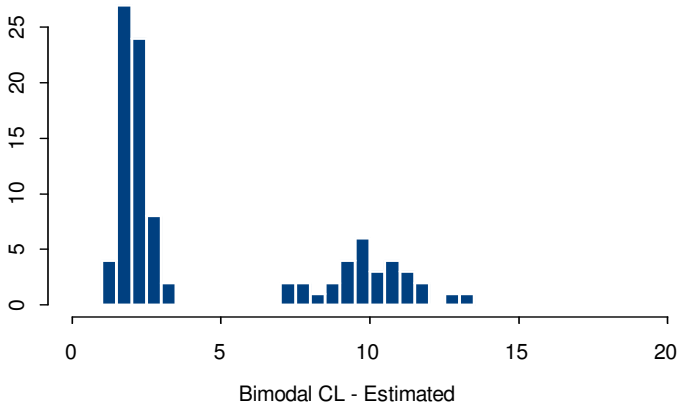
Can obviate the need for a $ABBREV record.

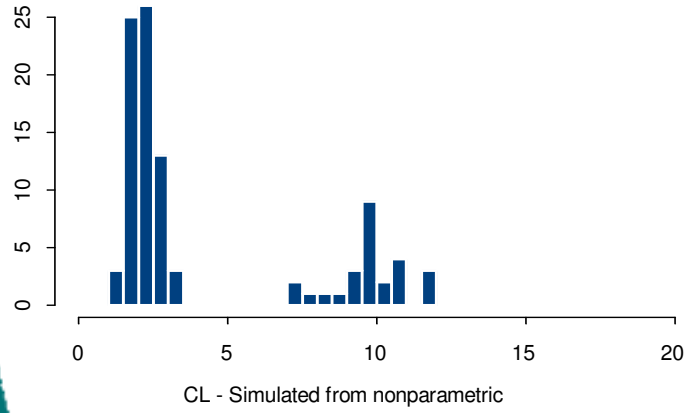
Features with little or no “official” documentation

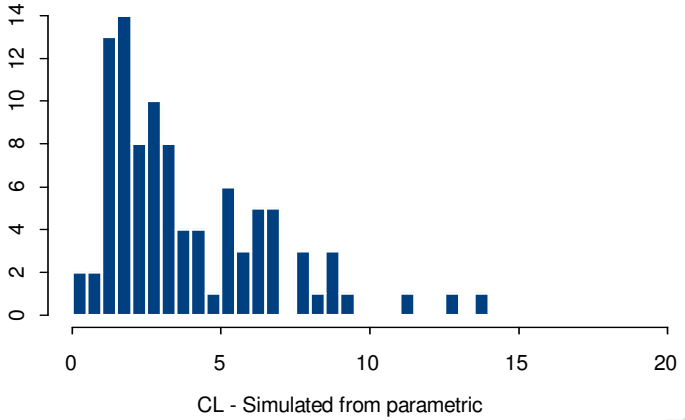
- $NONPARAMETRIC – estimate a nonparametric distribution for ETA’s. Could be useful for simulations.
- Stieltjes option on $ESTIM

NONPARAMETRIC –









NONMEM VI Distribution to Users

Late August or Early September 2006

Abbreviated Function Example

```
$PRED
   ...
   VECTRA(1)=THETA(1)*EXP(ETA(1))
   VECTRA(2)=TIME
   ...
   A=DOSE*FUNCA(VECTRA)
   ...
```

Abbreviated Function Example

```
FUNCTION FUNCA(X,X1,X2)
      DOUBLE PRECISION X,X1,X2,FUNCA,EXPT
      DIMENSION X(9),X1(9),X2(9,9)
C THE FUNCTION ITSELF
      EXPT=EXP(-X(1)*X(2))
      FUNCA=EXPT
C 1ST. PARTIALS
      X1(1)=-EXPT*X(2)
      X1(2)=-EXPT*X(1)
C 2ND. PARTIALS
      X2(1,1)=EXPT*X(2)*X(2)
      X2(1,2)=EXPT*X(1)*X(2)
      X2(2,1)=EXPT*X(1)*X(2)
      X2(2,2)=EXPT*X(1)*X(1)
      RETURN
      END
```