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Validation of Population Stochastic Modelling R Package in Comparison with NONMEM VI

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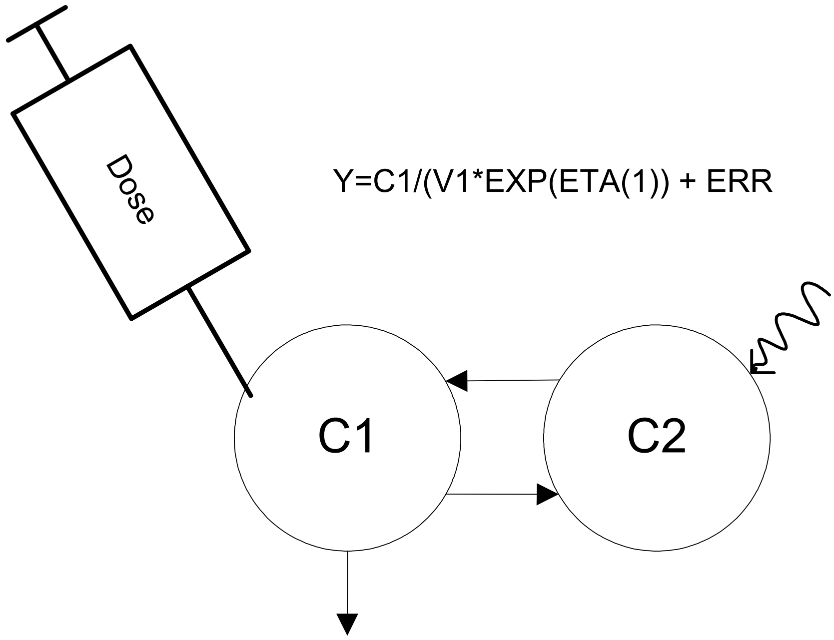
Introduction

This document describes the validation process of Population Stochacstic Modelling implemented in the R-package ***PSM.*** PSM is a software package for handling mixed-effects state-space models based on Stochastic Differential Equations (SDE). The package is currently limited to linear models but work has been put into a Fortran implementation for faster parameter estimation. A Non-Linear version is already in Beta-Version but is still being tested and improved.

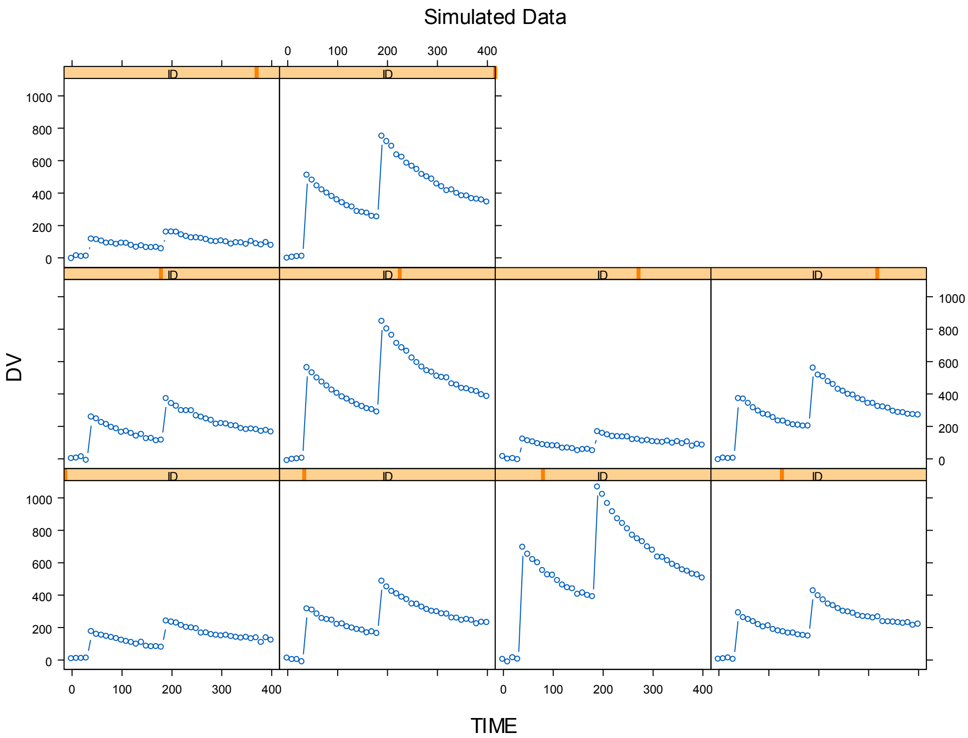
The process will validate the objective function calculation in PSM with respect to the objective function in NONMEM VI.

Data description

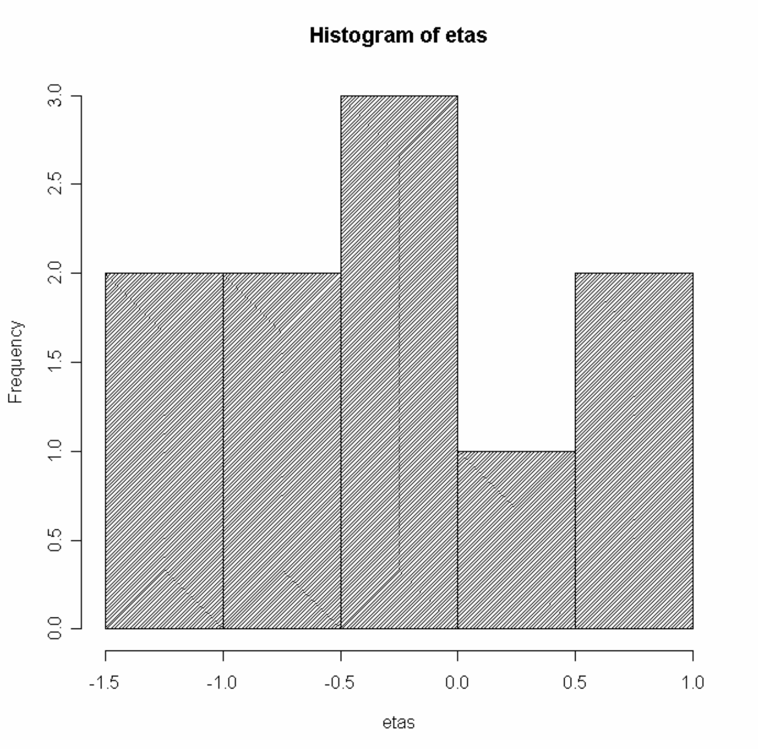
For the validation of the objective function simulated is being used. PSM is used to simulate data of 10 subjects with parameters as below.



SIG = 10
S = 40 -> W=SQRT(40)= 6.32
V1 = 7
OMEGA = 0.5



The distribution of used etas in the simulations can be seen below.



ODE Likelihood

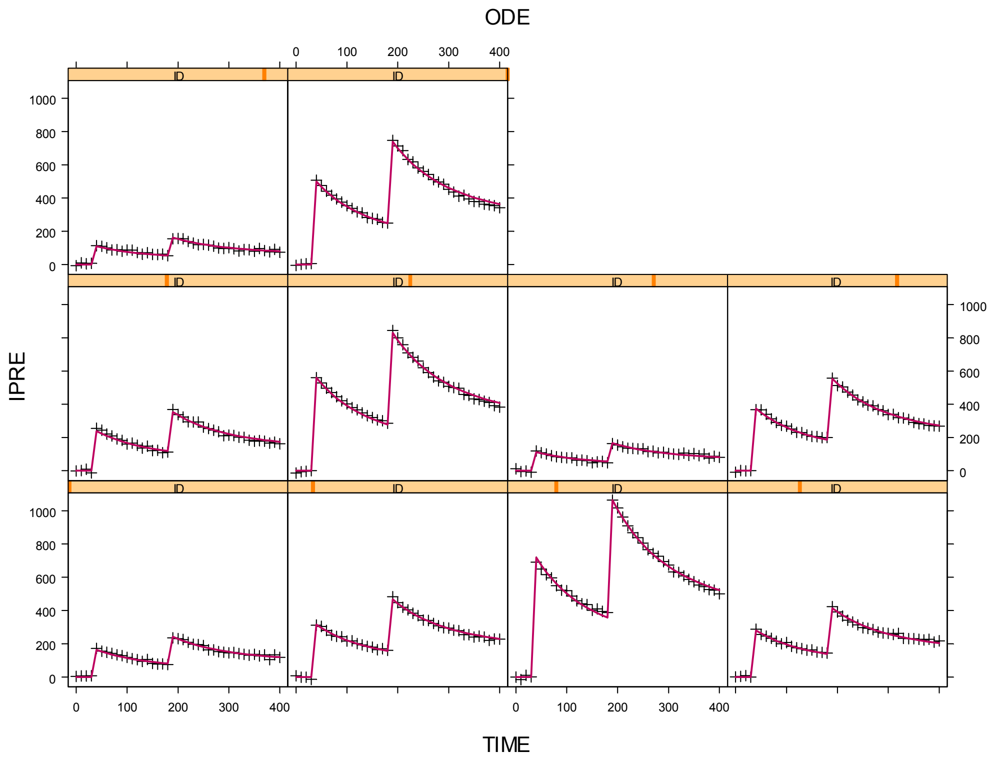
This part of the document deals with the comparison of the calculated likelihood value by assuming that the data can be modelled using a system of ordinary differential equations (ODE).

ODE in NONMEM

The described 2 compartment model was implemented as an ODE model in NONMEM. The modelling will thus not take into account the random fluctuations in compartment 2. The NONMEM Control File can be found in Appendix A.

The NONMEM Optimization gives the following result:

OFV: 2306.517
$THETA
W = 9.01
V1 = 4.97
OMEGA=0.384



1: Profiles from NONMEM ODE

Collapsed SDE in NONMEM

The same model is implemented in NONMEM once again but now as a system of stochastic differential equations (SDE) but collapsed into an ODE by setting SIG=0. The SDE NONMEM control file is generated by the use of Christoffer Tornøes S-Plus script [I].

OFV: 2306.518
$THETA
W = 9.01
V1 = 4.97
OMEGA=0.384

The estimated parameters are almost identical to the NONMEM ODE model with a difference on third digit in Objective Function Value.

Collapsed SDE in PSM

The 2-compartment model is also implemented in R using the package PSM. The model specification can be seen in Appendix C.
The likelihood is determined by using the population parameter estimates found in NONMEM. NONMEM only outputs parameter values with 2 digits which can be the cause of small differences.

The R function *APL.KF* from the PSM package is used to calculate the likelihood for given parameters.
OFV_{PSM} = 1530.031

PSM returns the negative loglikelihood but there is still a difference compared to NONMEM. This difference can be explained by the following formula [II]. The difference arises from the likelihood from the size of the dataset which is irrelevant in loglikelihood ratio test and thereby disregarded in NONMEM.

$$OFV_{NONMEM} = 2 \cdot OFV_{PSM} - \log(2\pi) * \sum n_i$$

Where n_i is the number of observations for subject *i.*

In this case the OFV from PSM corresponds to
OFV_{NONMEM} = 2*1530.031 – log(2*pi)*410 = 2306.533

This corrected OFV is not equal to the objective function value from NONMEM. It is the belief that the difference is due to rounded parameter output from NONMEM and the precision of the individual eta optimization. The difference between likelihood values is acceptable considering the implementation differences and the number of optimizations leading to the result.

SDE Likelihood

This section will compare likelihood values from models based on stochastic differential equations. It is the same 2-compartment model used earlier that is now analyzed using SDEs.

SDE in NONMEM

The SDE control stream in NONMEM used to create the collapsed ODE model is reused to estimate SDE parameters. It is almost the same NONMEM control stream as in Appendix D but with changed parameter values.

The NONMEM Optimization gives the parameter values.

```
OFV: 2070.289
$THETA
W = 6.11
V1 = 4.91
SIG =12.1
OMEGA = 0.369
```

SDE in PSM

The 2 compartment system is also set up in R using the PSM package. The estimated parameters from NONMEM are used to calculate the likelihood.

The negative likelihood from PSM is
OFV_{PSM} = 1411.909

In this case the OFV from PSM corresponds to

OFV_{NONMEM} = 2*1411.909 – log(2*pi)*410 = 2070.289

Parameter estimation in PSM

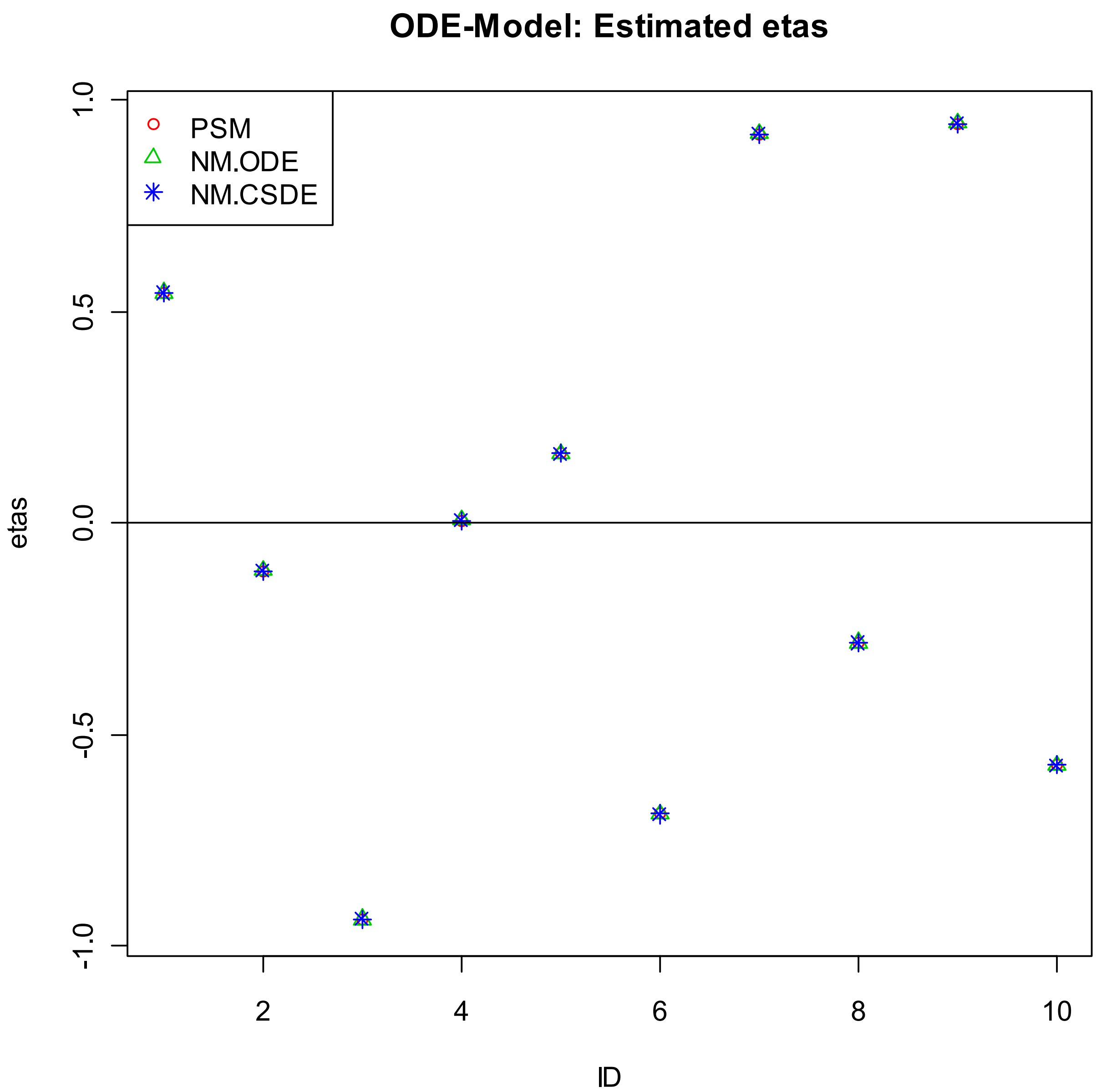
An additional validation of PSM was made by using PSM to estimate the parameters and then comparing parameter values. The starting point for the parameter estimation is identical to the one used in NONMEM.

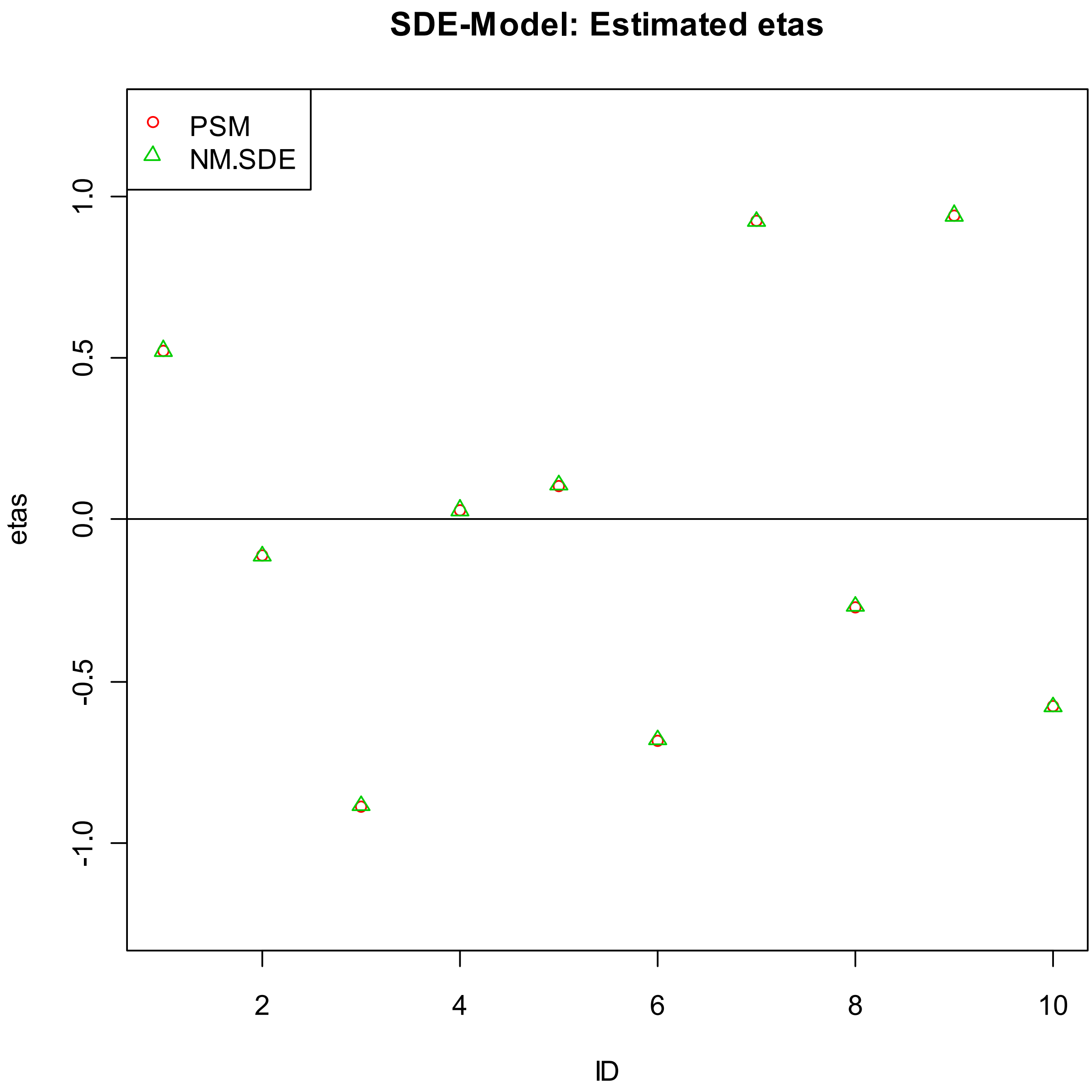
```
#                                          SIG    S       V1    OMEGA
> THETA <- list( LB=rep(0,4),  Init = c( 1 ,  9.01^2 , 4.97,  .5 ),      UB=rep(100,4))
> PSMout <- PSM.estimate(Model.SimDose, Est.Data, THETA,  trace = 0, optimizer = "optim")
$NegLogL
[1] 1411.909
$THETA
[1] 12.1009932   37.2782478    4.9052119    0.3693929
$sec
elapsed
  241.4
```

It can be seen that PSM is able to find parameter estimates identical to the parameters determined by NONMEM.

Estimated Etas

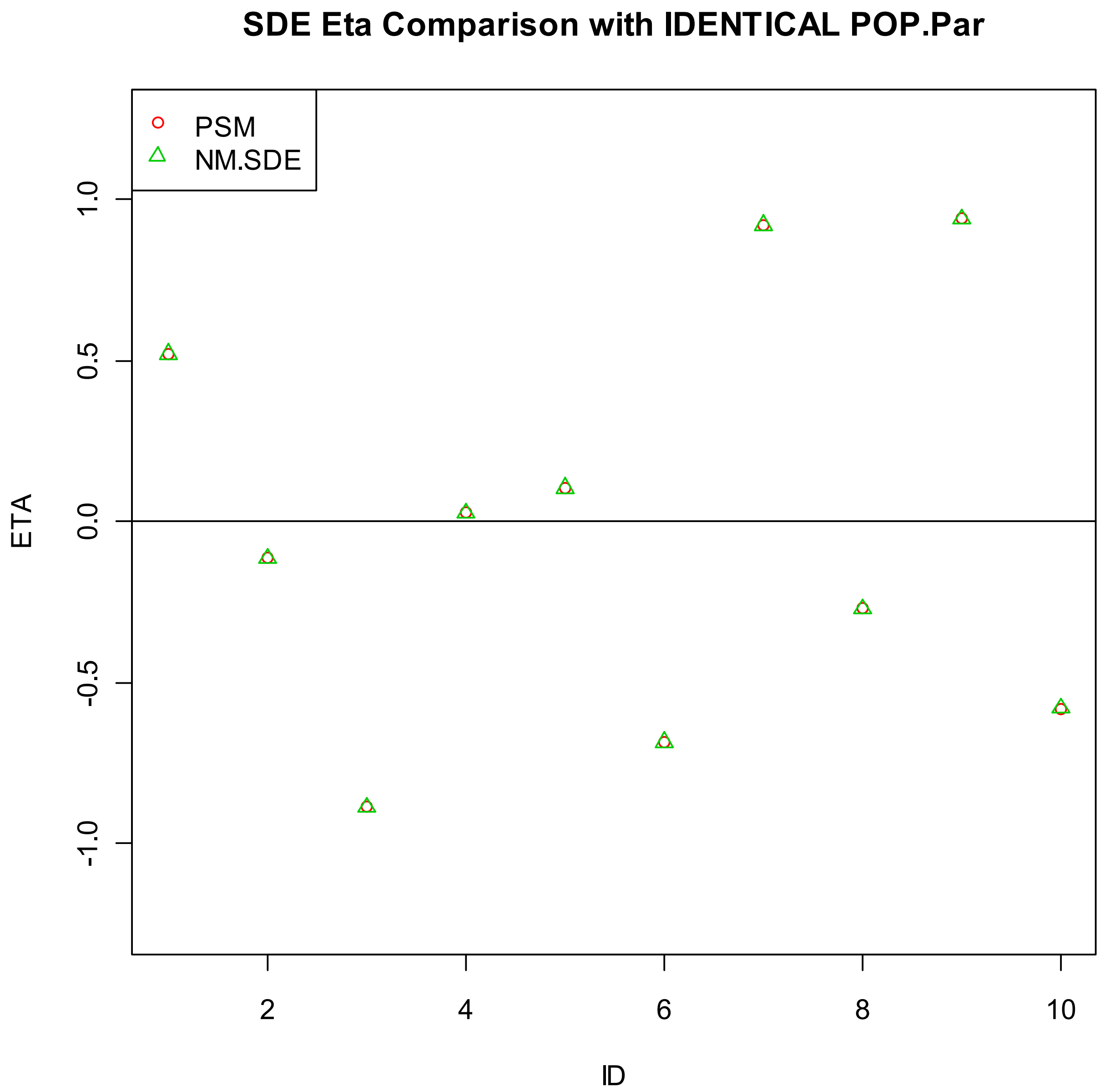
The plot below compares the etas found by estimation by the two programs. The precision used in the eta optimization in the FOCE approximation will influence the result of the comparison.





The two plots from the Ode- and SDE-model verify that PSM and NONMEM determines the same etas for same individual. The difference in ETA is corresponding to the accuracy of the optimizers.

Finally the etas are determined by reusing the parameters from the simulation.

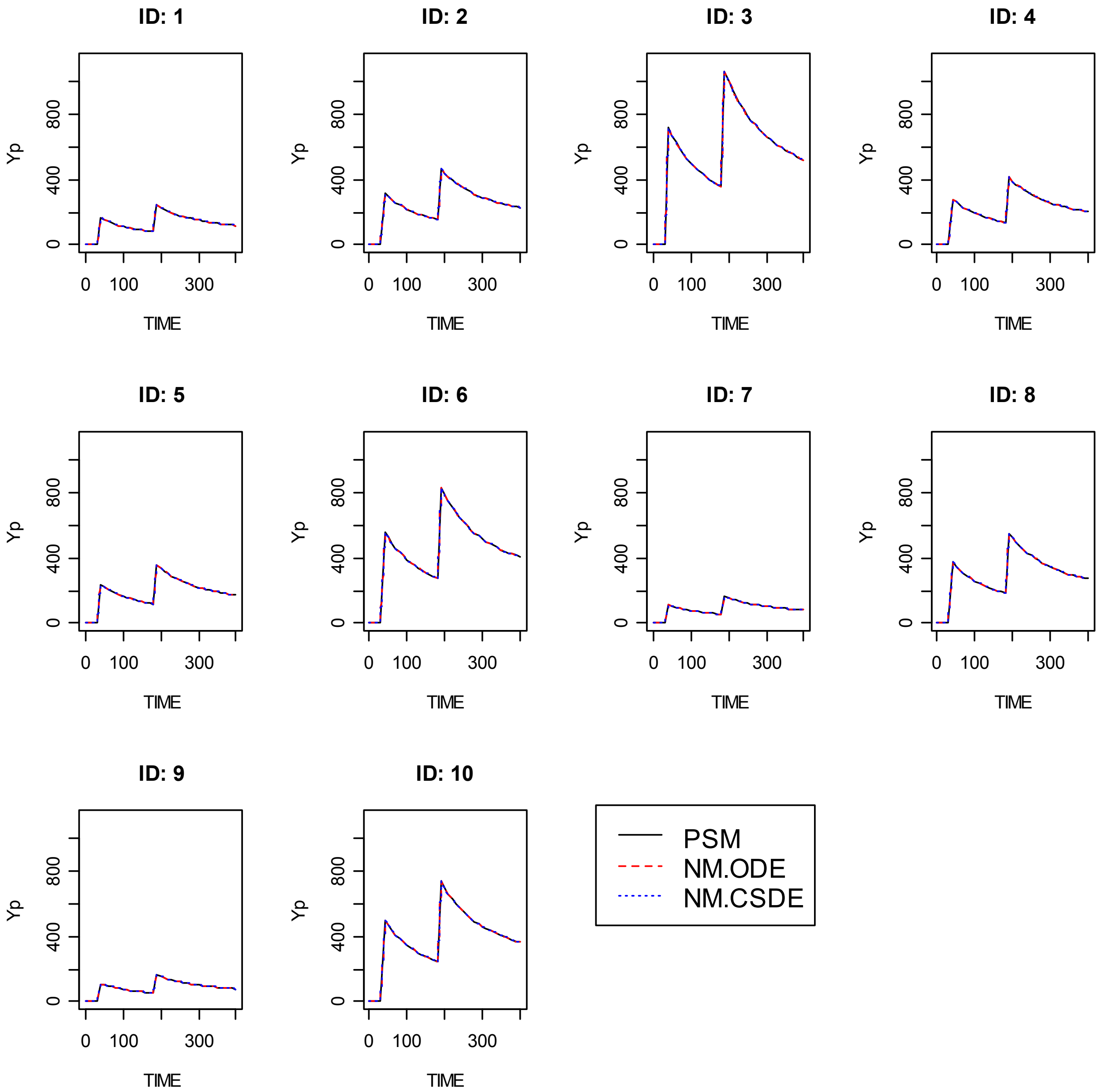


It can be seen that the simulated and estimated ETAS from PSM are very similar.

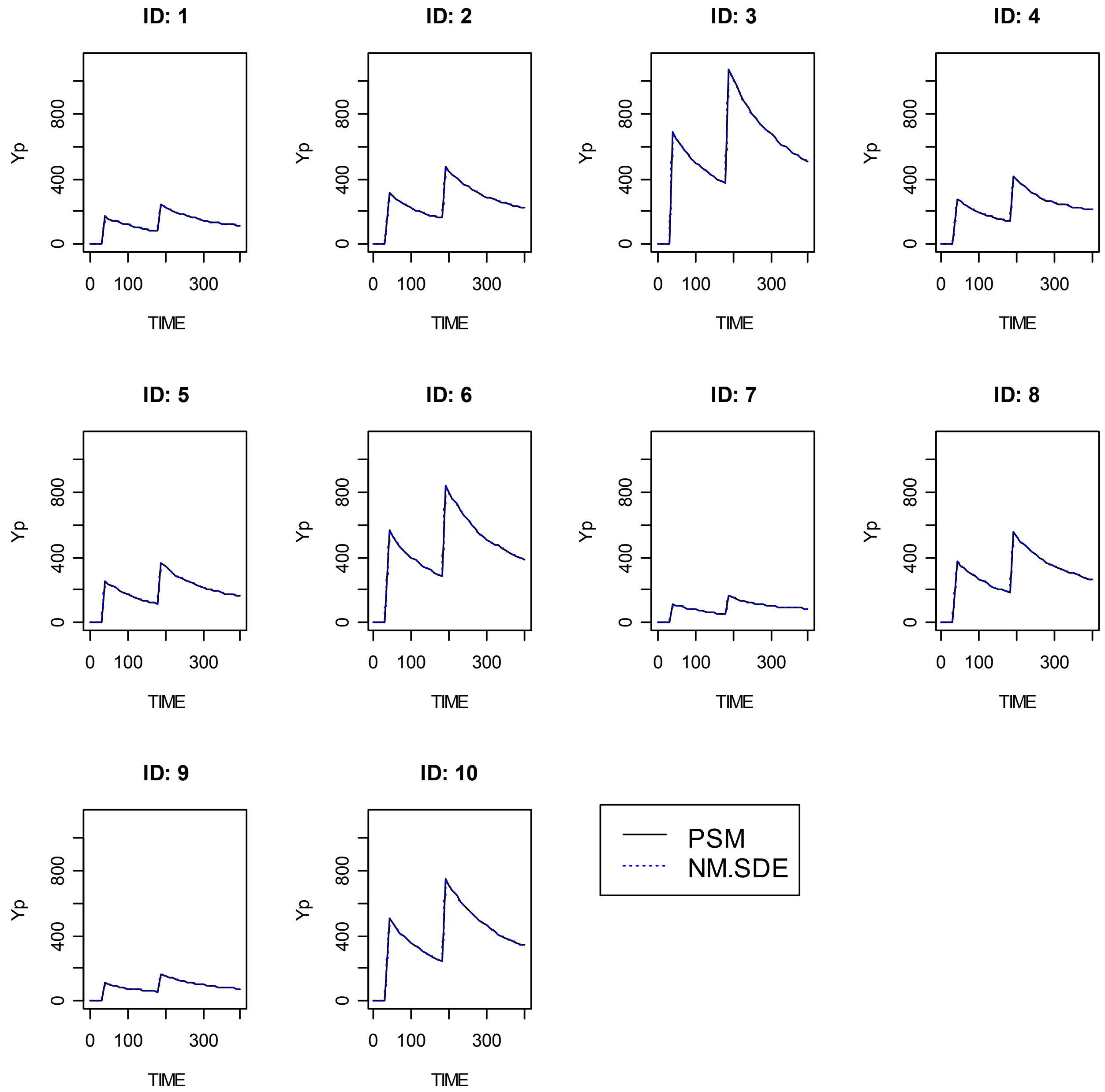
Profiles

The subjects' profiles are visually compared to check if any differences are found. First the three different ODE models are compared and afterwards the two SDE models.

ODE Observation Predicted



SDE Observation Predicted



Inspections of the plotted profiles show no sign of differences between the profiles originating from different models in different programs.

Likelihood Comparison

The likelihoods from the simulated data are compared between the different implementations in NONMEM and R. The corrected likelihoods are slightly different but it is believed that this is due to rounded parameter estimates from NONMEM that are used as input to R and the precision of the individual eta optimization.

Type	Model	NONMEM OFV	-LL	Corrected OBJ*	Parameters
ODE	NONMEM Pure	2306.517			W=9.01 V1=4.99 OMEGA=0.384
	NONMEM CSDE SIG=0	2306.518			W=9.01 V1=4.97 SIG=0.0 OMEGA=0.384
	PSM CSDE SIG=0		1530.031	2306.533	SIG=0 S=9.01^2 V1=4.97 OMEGA=0.384
SDE	NONMEM	2070.289			W=6.11 V1=4.91 SIG=12.1 OMEGA=0.369
	PSM Using NONMEM estimates		1411.909	2070.289	S=6.11^2 V1=4.91 SIG=12.1 OMEGA=0.369
SDE	PSM Optimized (Same init as NONMEM)		1411.909	2070.289	S=37.28 V1=4.91 SIG=12.1 OMEGA=0.369

***Corrected OFV** is due to NONMEMs objective function. The relation to PSM's likelihood is

$OBJ_{NONMEM} = 2*OBJ_{PSM}-\log(2*PI)*NoObs$ (NoObs=410)

Conclusion

The validation of PSM with respect to NONMEM VI showed results according to known differences in objective function values. This was the case for models based on ordinary and stochastic differential equations. The objective function from PSM or NONMEM can both be used for loglikelihood ratio testing of parameters as the difference is a constant and will cancel out.

Estimated etas and profiles with PSM and NONMEM were identical to the precision expected due to implementation differences.

The overall conclusion is that the objective function from PSM is validated with respect to NONMEM VI.

References

I. Tornøe, C. W.; Overgaard, R. V.; Agersø, H.; Nielsen, H. A.; Madsen, H. & Jonsson, E. N.
Stochastic differential equations in NONMEM: implementation, application, and comparison with ordinary differential equations.
Pharm Res, 2005, 22, 1247-1258

II. PSM Vignette
Found by installing PSM in R and executing
>vignette("PSM")

III. PSM Homepage
http://www.imm.dtu.dk/psm

Appendix

A. NONMEM ODE Control File

```
$PROBLEM PSMValidation

$INPUT ID TIME EVID DV CMT AMT

$DATA NONMEMinputdata.csv  IGNORE "

$SUBROUTINE ADVAN6 TOL 6 DP

$MODEL
COMP=(CENTRAL)
COMP=(PERIPH)


$THETA (0 0.6) ; W
$THETA (0 5 50) ; V1

$OMEGA 0.5     ; V1

$SIGMA 1 FIX

$PK
K1 = 0.005
K2 = 0.005
K3 = 0.002

V1 = THETA(2) * EXP(ETA(1))

$DES
DADT(1)= -(K1+K3)*A(1) + K2*A(2)
DADT(2)= K1*A(1)-K2*A(2)

$ERROR
IPRED=A(1)/V1
IRES=DV-IPRED
W=THETA(1)
IWRES=IRES/W
Y=IPRED+W*EPS(1)

$ESTIMATION MAXEVALS=9999 METHOD=1 INTERACTION NOABORT SIGDIGITS=3 PRINT=5

$COVARIANCE

$TABLE ID TIME EVID IPRED IRES IWRES W ETA(1)
       NOPRINT ONEHEADER FILE=TABLE.PAR
```

B. NONMEM ODE Data File

```
" ID  TIME  EVID  DV  CMT  AMT
1  0  0  3.36  .  .
1  0  1  .  1  0.001
1  10  0  5.308  .  .
1  20  0  5.821  .  .
1  30  0  7.131  .  .
1  30.001  1  .  1  1500
1  40  0  171.076  .  .
1  50  0  154.672  .  .
1  60  0  148.591  .  .
1  70  0  141.699  .  .
1  80  0  133.969  .  .
1  90  0  127.972  .  .
1  100  0  117.7  .  .
1  110  0  110.805  .  .
1  120  0  103.981  .  .
1  130  0  93.687  .  .
1  140  0  104.735  .  .
1  150  0  81.248  .  .
1  160  0  76.893  .  .
1  170  0  78.487  .  .
1  180  0  74.806  .  .
1  180.001  1  .  1  1500
1  190  0  235.905  .  .
1  200  0  229.751  .  .
1  210  0  224.651  .  .
1  220  0  208.735  .  .
1  230  0  196.997  .  .
1  240  0  194.471  .  .
1  250  0  189.882  .  .
1  260  0  163.172  .  .
1  270  0  163.315  .  .
1  280  0  152.015  .  .
1  290  0  148.89  .  .
1  300  0  144.371  .  .
1  310  0  147.981  .  .
1  320  0  140.777  .  .
1  330  0  135.921  .  .
1  340  0  130.942  .  .
1  350  0  136.108  .  .
1  360  0  127.482  .  .
1  370  0  133.208  .  .
1  380  0  104.487  .  .
1  390  0  133.335  .  .
1  400  0  118.148  .  .
2  0  0  7.616  .  .
2  0  1  .  1  0.001
2  10  0  -1.503  .  .
2  20  0  -2.192  .  .
2  30  0  -14.324  .  .
2  30.001  1  .  1  1500
.
.
```

C. PSM Model Specification

```
K12 <- 0.005
K21 <- 0.005
K10 <- 0.002  #[L/min]

Model.SimDose <- list(
               Matrices = function(phi) {
                 V1i <- phi[["V1"]]
                 matA <- matrix(c(-(K12+K10) ,  K21 ,
                                 K12 , -K21 ) ,nrow=2,byrow=T)
                 matC <- matrix(c(1/V1i,0),nrow=1)
                 list(matA=matA,matC=matC)
               },
               X0 = function(Time=Na,phi,U=Na) {
                 matrix(0,nrow=2)
               },
               SIG = function(phi) {
                 sig22 <- phi[["sig22"]]
                 matrix(c( 0,0,
                         0,sig22), nrow=2, byrow=T)
               },
               S = function(phi) {
                 matrix(phi[["S"]])
               },
               h = function(eta,theta,covar) {
                 phi <- theta
                 phi[["V1"]] <- phi[["V1"]]*exp(eta[1])
                 phi                    },
               ModelPar = function(THETA){
                 list(theta=list(sig22=THETA[1], S=THETA[2],V1=THETA[3]),
                      OMEGA=matrix(THETA[4]) )
               },
               Dose = list(
                 Time = c(30,180),
                 State = c(1,1),
                 Amount = c(1500,1500)
                 )
               )
```

D. NONMEM SDE Control File

```
$PROBLEM PSMValidation
$INPUT ID HOUR EVID DV CMT AMT MDV SDE TIME
$DATA NONMEMinputdata.csvSDE  IGNORE "
$SUBROUTINE ADVAN6 TOL 6 DP
$MODEL
COMP=(CENTRAL)
COMP=(PERIPH)
       COMP = (P1)
       COMP = (P2)
       COMP = (P3)

$THETA (0 9.01 )       ; W
$THETA (0 4.97 50)     ; V1
$THETA (0 1)           ; SGW2

$OMEGA 0.5     ; V1

$SIGMA 1 FIX

$PK
M1 = 0.005
M2 = 0.005
M3 = 0.002
V1 = THETA(2) * EXP(ETA(1))
SGW2 = THETA(3)

IF(NEWIND.NE.2) THEN
  AHT1 = 0
  AHT2 = 0
  PHT1 = 0
  PHT2 = 0
  PHT3 = 0
ENDIF

IF(EVID.NE.3) THEN
  A1 = A(1)
  A2 = A(2)
  A3 = A(3)
  A4 = A(4)
  A5 = A(5)
ELSE
  A1 = A1
  A2 = A2
  A3 = A3
  A4 = A4
  A5 = A5
ENDIF

IF(EVID.EQ.0) OBS = DV

IF(EVID.GT.2.AND.SDE.EQ.2) THEN
  RVAR = A3/(V1**2)+THETA(1)**2
  K1   = A3*(1/V1)/RVAR
  K2   = A4*(1/V1)/RVAR
  AHT1 = A1 + K1*(OBS -(A1/V1))
  AHT2 = A2 + K2*(OBS -(A1/V1))
```

```
  PHT1 = A3 - K1*RVAR*K1
  PHT2 = A4 - K1*RVAR*K2
  PHT3 = A5 - K2*RVAR*K2
ENDIF

IF(EVID.GT.2.AND.SDE.EQ.3) THEN
  AHT1 = A1
  AHT2 = A2
  PHT1 = 0
  PHT2 = 0
  PHT3 = 0
ENDIF

IF(EVID.GT.2.AND.SDE.EQ.4) THEN
  AHT1 = 0
  AHT2 = 0
  PHT1 = A3
  PHT2 = A4
  PHT3 = A5
ENDIF

IF(A_0FLG.EQ.1) THEN
  A_0(1) = AHT1
  A_0(2) = AHT2
  A_0(3) = PHT1
  A_0(4) = PHT2
  A_0(5) = PHT3
ENDIF

$DES
DADT(1)= -(M1+M3)*A(1) + M2*A(2)
DADT(2)= M1*A(1)-M2*A(2) + 0
DADT(3) = (-(M1+M3))*(A(3))+(M2)*(A(4))+(-(M1+M3))*(A(3))+(M2)*(A(4))
DADT(4) = (-(M1+M3))*(A(4))+(M2)*(A(5))+(M1)*(A(3))+(-M2)*(A(4))
DADT(5) = (M1)*(A(4))+(-M2)*(A(5))+(M1)*(A(4))+(-M2)*(A(5))+SGW2*SGW2

$ERROR
IPRED=A(1)/V1
IRES=DV-IPRED
W=SQRT(A(3)/(V1**2)+THETA(1)**2)
IWRES=IRES/W
Y=IPRED+W*EPS(1)
$ESTIMATION MAXEVALS=9999 METHOD=1 INTERACTION NOABORT SIGDIGITS=3 PRINT=5
$COVARIANCE
$TABLE ID TIME EVID IPRED IRES IWRES W ETA(1)
       NOPRINT ONEHEADER FILE=TABLE.PAR
```

E. NONMEM SDE Data File

```
" ID TIME EVID DV CMT AMT MDV SDE NTIME
 1  -10.000 1       . 1 0.001 1 0   0.000
 1    0.000 0       . .    . 1 4  10.000
 1    0.000 2       . .    . 1 4  10.000
 1    0.000 3       . .    . 1 4  10.000
 1    0.000 1       . 1 0.001 1 0  10.000
 1    0.000 0    3.36 .    0 0 1  10.000
 1    0.000 2       . .    . 1 2  10.000
 1    0.000 3       . .    0 1 2  10.000
 1   10.000 0   5.308 .    0 0 1  20.000
 1   10.000 2       . .    . 1 2  20.000
 1   10.000 3       . .    0 1 2  20.000
 1   20.000 0   5.821 .    0 0 1  30.000
 1   20.000 2       . .    . 1 2  30.000
 1   20.000 3       . .    0 1 2  30.000
 1   30.000 0   7.131 .    0 0 1  40.000
 1   30.000 2       . .    . 1 2  40.000
 1   30.000 3       . .    0 1 2  40.000
 1   30.001 1       . 1  1500 1 0  40.001
 1   40.000 0 171.076 .    0 0 1  50.000
 1   40.000 2       . .    . 1 2  50.000
 1   40.000 3       . .    0 1 2  50.000
 1   50.000 0 154.672 .    0 0 1  60.000
 1   50.000 2       . .    . 1 2  60.000
 1   50.000 3       . .    0 1 2  60.000
 1   60.000 0 148.591 .    0 0 1  70.000
 1   60.000 2       . .    . 1 2  70.000
 1   60.000 3       . .    0 1 2  70.000
 1   70.000 0 141.699 .    0 0 1  80.000
 1   70.000 2       . .    . 1 2  80.000
 1   70.000 3       . .    0 1 2  80.000
 1   80.000 0 133.969 .    0 0 1  90.000
 1   80.000 2       . .    . 1 2  90.000
 1   80.000 3       . .    0 1 2  90.000
 1   90.000 0 127.972 .    0 0 1 100.000
 1   90.000 2       . .    . 1 2 100.000
```