NONMEM NON-INFLUENTIAL CORRELATED ETAs BUG AND HOW TO FIX IT

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Introduction

- Discovered by Nick Holford and Diane Mould[1] who used NONMEM to estimate correlation between covariates and impute missing covariates
- Described by Stuart Beal[2]
- Affects conditional estimation methods (FOCE+/- INTERACTION, LAPLACIAN, HYBRID and POSTHOC step of FO)

[1] N. Holford, D. Mould, NONMEM model for imputation of missing covariates.

[2] S. Beal, 14 Nov 2002 contribution to the NONMEM user group.

Introduction

- Bug influences the conditional estimation step when NONMEM estimates random effects (ETAs) using individual data and estimates of population parameters (THETA, OMEGA, SIGMA)

- Bug occurs only under special conditions

Introductory Example

1. PK model with oral and IV doses, where some individuals receive only IV dose
2. Random effects on KA (ETA1) and CL (ETA2)

```
$PK
    KA  =  THETA(1)*EXP(ETA(1))
    CL  =  THETA(2)*EXP(ETA(2))
    V2  =  THETA(3)
```

Possible Scenarios

CASE 1 (not affected by the bug)

- No correlation between random effects
- For individuals who are given only the IV dose, KA cannot be estimated from the data; KA is assumed to be equal to the population value (ETA(1)=0).

CASE 2 (affected by the bug)

- Correlation between random effects

  $OMEGA BLOCK(2)

Correct Behavior

- For individuals with only IV dose, KA cannot be estimated from the data; however, individual CL (i.e., ETA(2)) can be estimated.
- Although there are no data that would allow direct estimation of KA (ETA(1)), NONMEM can use a known correlation matrix (OMEGA) and estimates of CL to obtain individual estimate of KA.
- The individual estimate of KA is NOT equal to the population value (ETA(1) ≠0).

Bug

- KA is assigned a value that is equal to the population value (ETA(1)=0), even though the model structure includes correlation between ETA(1) and ETA(2).

Effects of the Bug

METHOD=0 POSTHOC

Incorrect estimates of individual parameters

METHOD=1 (FOCE, LAPLACIAN) or HYBRID

Incorrect estimates of population and individual parameters

Overview

- Conditions leading to the bug's appearance
- Examples of non-influential ETAs
- Non-influential versus non-identifiable ETAs
- How to check whether the bug has affected your solution
- Zeta-transformation fix (S. Beal)
- Negligible Influence Correction fix with examples
- Summary

Conditions Necessary for the Bug to Affect the Results

The bug may influence the solution when all three of the following conditions are met:

1. Conditional estimation is used.

   METHOD=1 or HYBRID

   or

   METHOD=0 POSTHOC

Conditions Necessary for the Bug to Affect the Results

2. The model contains at least one non-influential ETA.

   Non-influential = ETA does not affect the model prediction for a particular individual

Conditions Necessary for the Bug to Affect the Results

3. Non-influential ETA is correlated with influential ETAs.

   Non-influential ETA is included in $OMEGA BLOCK(n)

Example 1
KA Estimates: Individuals with IV Data Only

```
$INPUT
 ; For some individuals, only IV (compartment 2) dose is
   given.
$PK
   KA  =  THETA(1)*EXP(ETA(1))
   CL  =  THETA(2)*EXP(ETA(2))
   V2  =  THETA(3)*EXP(ETA(3))
$ERROR
   Y=F + ERR(1)
$OMEGA BLOCK(3)
```

Example 1
KA Estimates: Individuals with IV Data Only

- For individuals receiving only an IV dose, ETA(1) is non-influential.

- Known exceptions:

  For this particular problem the bug does not affect ADVAN5 and ADVAN7

Example 2
Estimation of Missing Covariates

```
$INPUT ID HT WT DV CODE
$PRED
   IWT = THETA(1)*EXP(ETA(1))  + ERR(1)
   IHT  = THETA(2)*EXP(ETA(2))  + ERR(2)
   IF (CODE=1) Y=IWT
   IF (CODE=2) Y=IHT
$OMEGA BLOCK(2)
```

If WT is missing, ETA(1) is non-influential

If HT is missing, ETA(2) is non-influential

Example 3
Estimation of a PK/PD Relationship with Placebo Effect

```
$PRED
   PLAC = THETA(1)*EXP(ETA(1))
   EFF  = THETA(2)*EXP(ETA(2))*CONC
   Y=PLAC+EFF+ERR(1)

$OMEGA BLOCK(2)
```

- For placebo individuals, CONC = 0, and ETA(2) is non-influential.

Example 4
Simultaneous Estimation of PK/PD Model When Missing PD Data for Some Individuals

```
$PK
   K     =  THETA(1)*EXP(ETA(1))
   V1    =  THETA(2)*EXP(ETA(2))
   K12 =  0.001*K                          ; KE0
   K21 = THETA(3)*EXP(ETA(3))
   V2    = K12*V1/K21                       ; effect compartment volume
   SLOP= THETA(4)*EXP(ETA(4))     ; PK/PD model
$ERROR
   CE=A(2)/V2   ; CE is the effect compartment concentration
   IF( PK observation) Y = A(1)/V1+ERR(1)
   IF( PD observation) Y =SLOP*CE+ERR(2)
$OMEGA BLOCK(4)
```

Example 4

Simultaneous Estimation of the PK/PD Model When Missing PD Data for Some Subjects

- When PD data are missing, ETA(4) is non-influential.
- ETA(3) is still influential !!!

  (ETA(3) affects PK, although mass transfer is negligible)

Example 5

Parent-Metabolite Model When Metabolite Data Are Not Available for Some individuals

```
$PK
;parent model
   V1   = THETA(1)*EXP(ETA(1))
   K12  = THETA(2)      ; rate of metabolism
; metabolite model
   V2   = THETA(3)*EXP(ETA(2))
   K20 = THETA(4)       ; elimination rate
```

- ETA2 is non-influential when metabolite data are not available.

Non-Influential vs. Non-Identifiable

- Non-Influential (for an individual):

  Partial derivative of the model prediction (Y) w.r.t. ETA is exactly zero.

- Non-Identifiable:

  Partial derivative of the model prediction (Y) w.r.t. ETA is very small, so that large changes in the parameter value lead to negligible changes in the prediction.

Non-Identifiable but Influential

1.PK Model

- No samples during absorption phase:

  ETA on KA is not identifiable but influential as long as there is an oral dose.

- Samples at steady-state trough only:

  ETA on V is not identifiable but influential.

Non-Identifiable but Influential

2. EMAX PK-PD Model

- Data at *high* CE (>> EC50) only:

  ETA on EC50 is influential.

- Data at *low* CE (<< EC50) only:

  ETA on EMAX is influential.

Has Your Solution Been Affected?

1. Output correlated ETAs in $TABLE.
2. If some of these ETAs are exactly zero for some individuals, while others are not exactly zero for the same individuals, investigate the problem. Chances are that the ETA-bug influenced the model.

- For each individual, correlated ETAs should be all zero or non-zero at the same time. It is highly unlikely that a correct estimate of one of the correlated ETAs is exactly zero, while other ETAs have non-zero values.

Effect of the Bug on Parameters

Example: Oral/IV Dose Study

- Data were simulated for 20 individuals.
- Half received an oral dose of 100 mg.
- Half received an IV dose of 100 mg.

Effect of the Bug on Parameters

Parameter	True value	Estimates		
		FO	FOCE (bug)	FOCE (fixed)
KA	0.05	0.036	0.045	0.047
CL	0.06	0.056	0.059	0.059
V2	0.8	0.55	0.70	0.69
K23	0.07	0.084	0.073	0.073
K32	0.06	0.058	0.061	0.061
$OMEGA_{11}$	0.36	0.59	0.28	0.64
$OMEGA_{12}$	0.23	0.37	0.098	0.38
$OMEGA_{22}$	0.16	0.23	0.22	0.23
$OMEGA_{13}$	0.29	0.48	0.12	0.48
$OMEGA_{23}$	0.19	0.29	0.27	0.28
$OMEGA_{33}$	0.25	0.41	0.35	0.37
SIGMA	0.04	0.065	0.039	0.039

How Can the Bug Be Fixed?

IDEA: Make all ETAs influential.

Method 1:

ZETA transformation (suggested by Stuart Beal)

CORR= ETA(1)+…+ETA(n)

ZETAi= 0.5*ETA(i)+0.5*CORR, i = 1,n

Method 1: ZETA-transformation

Example:

```
$PK
   CORR=0.5*(ETA(1)+ETA(2)+ETA(3))
   ZETAi = 0.5*ETAi +CORR
   KA  =  THETA(1)*EXP(ZETA1)
   CL  =  THETA(2)*EXP(ZETA2)
   V2  =  THETA(3)*EXP(ZETA3)
```

- If *at least one* ZETA is influential, then <u>all</u> ETAs are influential.

ZETA-transform in Matrix Notation

ZETA= B*ETA, ETA =A * ZETA, $A=B^{-1}$,

B(I,I)=1; B(I,J) = 1/2, (I ≠ J)

A(I,I)=2n/(n+1); A(I,J) = -2/(n+1) (I ≠ J)

Initial Estimates of OMEGA block:

Original: OMEGAini

Z-transformed: ZOMEGAini = A*OMEGAini*A

Final Estimates of OMEGA block

Z-transformed: ZOMEGA

Original: OMEGA = B*ZOMEGA*B

S-PLUS Code for ZETA-transform

```
# assign size of the OMEGA block
    n <- 3
#define matrices A and B
   B <- matrix(0.5,n,n)+0.5*diag(n)
   A <- ginverse(B)
# type all n2 elements of initial values for OMAGA matrix
   OMEGAini  <- matrix(c(...insert elements…),n,n)
# Compute initial values in ZETA-form
  ZOMEGAini <- A%*% OMEGAini%*%A
#              Fit NONMEM model
# type all n2 elements of the ZETA final estimates
  ZOMEGA <- matrix(c(...insert elements…),n,n)
# Compute final estimates of the OMEGA matrix
   OMEGA <- B%*% ZOMEGA%*%A
```

Method 2: Negligible Influence Correction

KK1 = 0.1**20

(Make it as small as needed to ensure no influence)

CORR= KK1 * (ETA(1)+…+ETA(n))

- Add CORR where it will be influential for all individuals, e.g.,:

  V in PK models;

  Y in PK-PD models

Oral/IV data Example

```
$PK
; only ETA(1) was non-influential for some
   individuals
   CORR= 0.1**20*ETA(1)
   KA  =  THETA(1)*EXP(ETA(1))
   CL  =  THETA(2)*EXP(ETA(2))
   V2  =  THETA(3)*EXP(ETA(3)+ CORR)
$OMEGA BLOCK(3)
```

Estimates of Missing Covariates Example

```
$PRED
  CORR=0.1**20*(ETA(1)+ETA(2))
   IWT = THETA(1)*EXP(ETA(1))  + ERR(1)
   IHT  = THETA(2)*EXP(ETA(2)) + ERR(2)
   IF (CODE=1) Y= IWT + CORR
   IF (CODE=2) Y= IHT  + CORR
$OMEGA BLOCK(2)
```

PK/PD and Placebo Effects Example

```
$PRED
  CORR= 0.1**20*(ETA(1)+ETA(2))
  PLAC = THETA(1)*EXP(ETA(1))
  EFF   = THETA(2)*EXP(ETA(2))*CONC
  Y = PLAC+EFF+ERR(1)+CORR
$OMEGA BLOCK(2)
```

Summary

- Impact of non-influential correlated ETA bug can be important but the bug is easily identified.
- Non-influential should not be confused with non-identifiable
- The most significant effect seems to be an under-estimation of the variances and covariances of non-influential ETAs
- Fixes are implemented with user-code in NMTRAN control stream
- Results obtained using ZETA-transformation and Negligible Influence Correction methods should be identical up to the numerical precision. This was checked for all examples included in this presentation

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