EFFECT OF NONMEM MINIMIZATION STATUS AND NUMBER OF REPLICATES ON BOOTSTRAP PARAMETER DISTRIBUTIONS FOR POPULATION PHARMACOKINETIC MODELS: A CASE STUDY

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Introduction

- Bootstrap (BS) parameter distributions are often used to characterize estimation uncertainty and determine confidence intervals (CI) for population pharmacokinetic (PPK) model parameters[1,2,3].
- These results are used to guide inferences about clinical relevance of covariate effects and other model components.
- The PPK estimation method minimization status and number of bootstrap replicates may impact the resulting confidence intervals for PPK models.
- The goal of this work was to compare BS parameter distributions using a published PPK model for oxaprozin[4] (OX) under varying conditions of:
    - Minimization Status
    - Number of BS Replicates

Methods

- Given a final PPK model and data set for OX, nonparametric BS analyses were conducted.
- 2400 replicate data sets were generated from the original data by re-sampling with replacement, using the individual as the sampling unit, and stratifying on important covariate factors (e.g. sex, and adult vs. pediatric disease state)
- PPK parameter estimates for each replicate data set were obtained by nonlinear mixed effects modeling with NONMEM V level 1.1[5] (with $ESTIMATION and $COVARIANCE steps)
- BS data sets and summaries were generated using S-PLUS (6.1 Pro/Win, Insightful, Seattle, WA), and automation of NONMEM for repeated estimation runs was accomplished using Perl (5.8.4., www.cpan.org) and a NONMEM INFN subroutine. Computations were done on Intel-based PC workstations under the WinXP operating system.

Methods

- Resulting BS parameter distributions were summarized by:

  – Minimization Status

  ALL: All estimation runs reporting parameter estimates

  MIN: Estimation runs with successful minimization

  COV: Estimation runs with successful MIN and $COV step

  – Number of BS Replicates

  200, 500, 1000, 1500 or 2400

- BS 95% CI were calculated as the 2.5^{th} and 97.5^{th} quantiles of the BS parameter distributions across replicates for each PPK parameter

The Model

```
$PROB 003,  Oxaprozin Example
$INPUT ID DOSE AMT SS II EVID MDV STIM TIME TIM2
    CU CT DV=LCU LCT JRA AGE SEX WT BSA ALBU
$DATA nonmem.dat
$SUBR ADVAN2 TRANS2 INFN=runlog3.for
$PK
  Q600=0
  IF (DOSE .EQ. 600) Q600=1
  TVTLAG=Q600*THETA(1)+(1-Q600)*THETA(2)
  TVKA=Q600*THETA(3)+(1-Q600)*THETA(4)
  TVV=Q600*THETA(5)+(1-Q600)*THETA(6)
  TVCL=Q600*THETA(7)+(1-Q600)*THETA(8)
  TLAG=TVTLAG*EXP(ETA(1))
  WT70=WT/70
  KAJRA=(1+THETA(9))**JRA
  KASEX=(1+THETA(10))**SEX
  KAWT=WT70**THETA(11)
  KA=TVKA*KAJRA*KAWT*KASEX*EXP(ETA(2))
  VJRA=(1+THETA(12))**JRA
  VSEX=(1+THETA(13))**SEX
  VWT=WT70**THETA(14)
  V=TVV*VJRA*VWT*VSEX*EXP(ETA(3))
  CLJRA=(1+THETA(15))**JRA
  CLSEX=(1+THETA(16))**SEX
  CLWT=WT70**THETA(17)
  CL=TVCL*CLJRA*CLWT*CLSEX*EXP(THETA(19)*ETA(3))
  ALAG1=TLAG
  S2=V/1000
$ERROR
  SDE=SQRT(THETA(18))
  Y=LOG(F)+SDE*EPS(1)
  IPRE=F
  IWRE=(LCU-LOG(F))/SDE
$THETA
  (0, 0.71, 0.95)    ;KEEP 1 TLAG-600
  (0, 0.80, 0.95)    ;KEEP 2 TLAG-1200
  (0, 4.0, )         ;KEEP 3 KA-600
  (0, 1.5, )         ;KEEP 4 KA-1200
  (100, 1800, )      ;KEEP 5 V-600
  (100, 1100, )      ;KEEP 6 V-1200
  (10, 100, 500)     ;KEEP 7 CL-600
  (10, 85, 500)      ;KEEP 8 CL-1200
  (-0.7, 0.2,)       ;9 JRA effect on KA
  (-0.7, -0.3,)      ;10 SEX effect on KA
  (-0.5, 2.0,)       ;11 WT effect on KA
  (-0.7, 0.2,)       ;12 JRA effect on V
  (-0.7, -0.1,)      ;13 SEX effect on V
  (-0.5, 1.5,)       ;14 WT effect on V
  (-0.7, -0.1,)      ;15 JRA effect on CL
  (-0.7, 0.1,)       ;16 SEX effect on CL
  (-0.5, 1.0,)       ;17 WT effect on CL
  (0, 0.05, )        ;KEEP 18 VAR(EPS)
  (0.1, 1.1,)        ;KEEP 19 Variance Ratio CL
    to V
$OMEGA DIAGONAL(2)
  0. FIXED; VAR(TLAG)
  1.5; VAR(KA)
$OMEGA BLOCK(1)
  0.15; VAR(V)
$SIGMA DIAGONAL(1)
  1.0 FIXED;
$EST MAXEVAL=9999 PRINT=10 METHOD=1 NOABORT
$COV PRINT=E
```

Results

- Some BS estimation attempts terminated without reporting any parameter estimates (28% of replicates)
- The percentage of total (2400) replicates by category was:

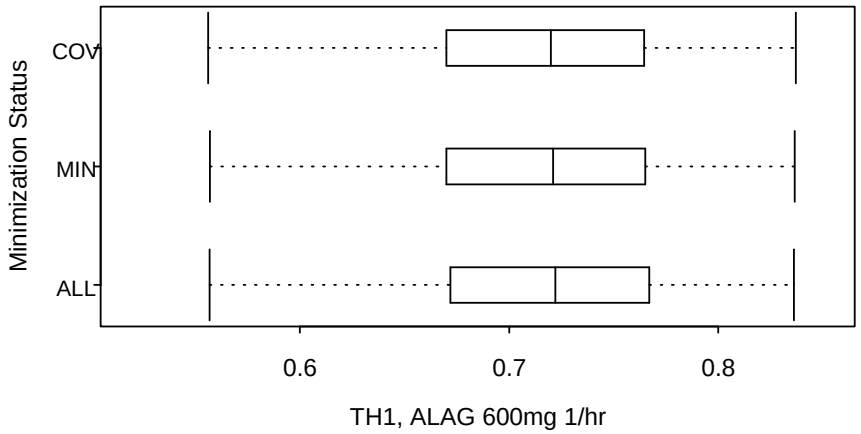
  ALL: 72%

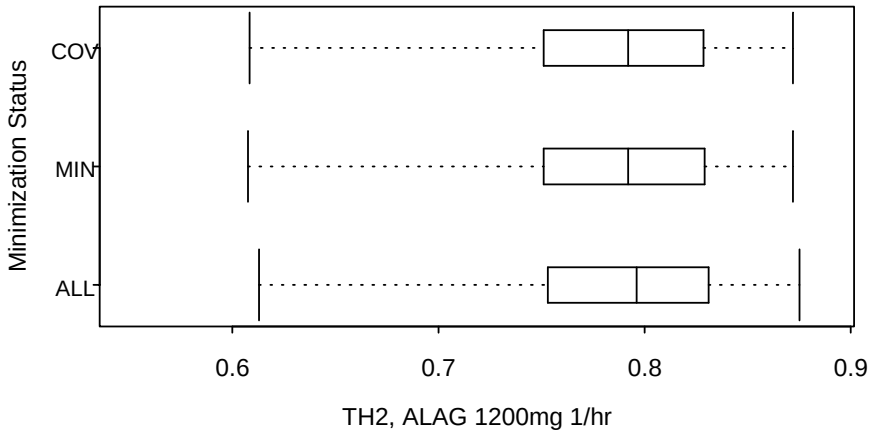
  MIN: 61%

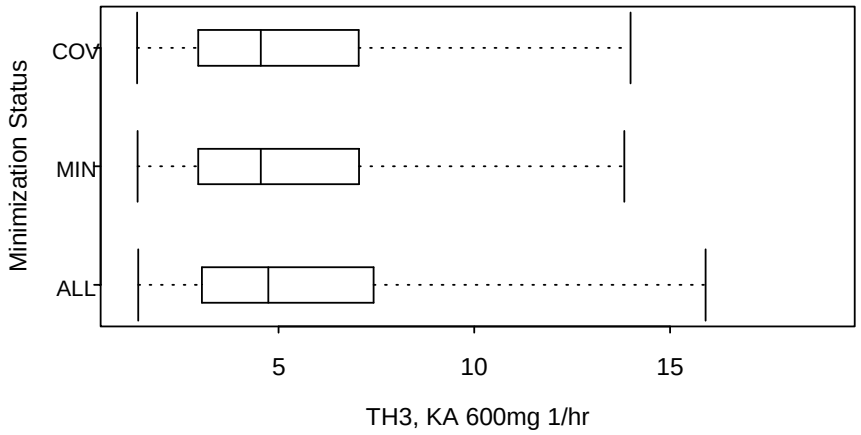
  COV: 60%
- The dependence of BS parameter distributions on minimization status is illustrated in Figure 1 (box plots) and Table 1 (percent change in 95% CI)
- The dependence of BS parameter distributions on number of replicates is illustrated in Figure 2 (box plots) and Table 2 (percent change in 95% CI)

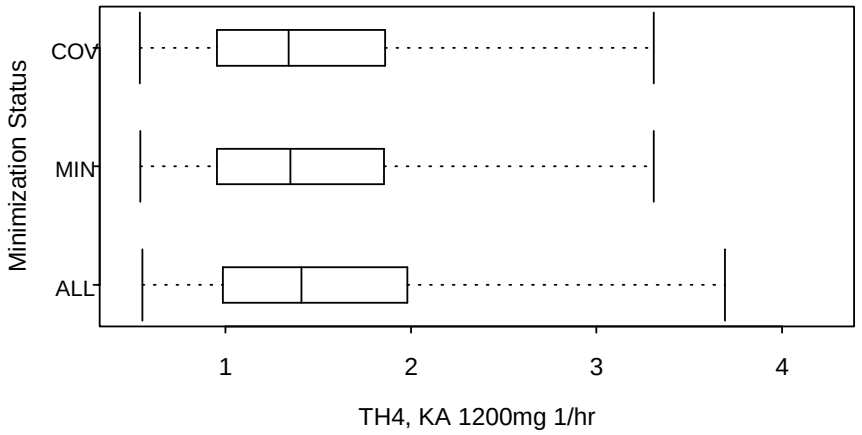
Figure 1: Effect of Minimization Status on BS Parameter Distributions

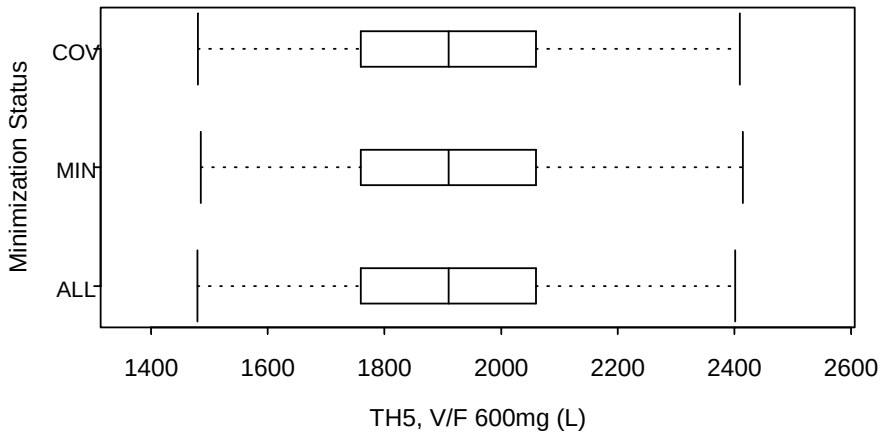
- Box plots representing resulting BS parameter distributions are presented for each model parameter, by minimization status category (ALL, MIN or COV).
- Whiskers indicate the 95% CI, the box indicates the inter-quartile range, and the vertical line in the box indicates the median of the parameter distribution

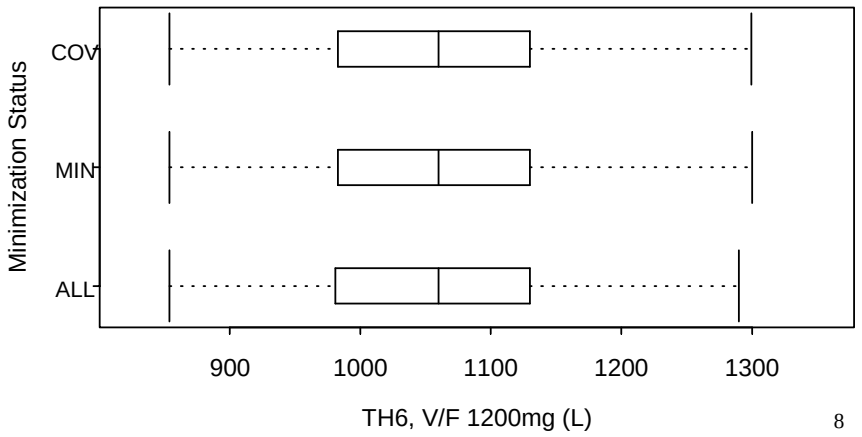

Minimization Status
COV
MIN
ALL
0.6
0.7
0.8
TH1, ALAG 600mg 1/hr

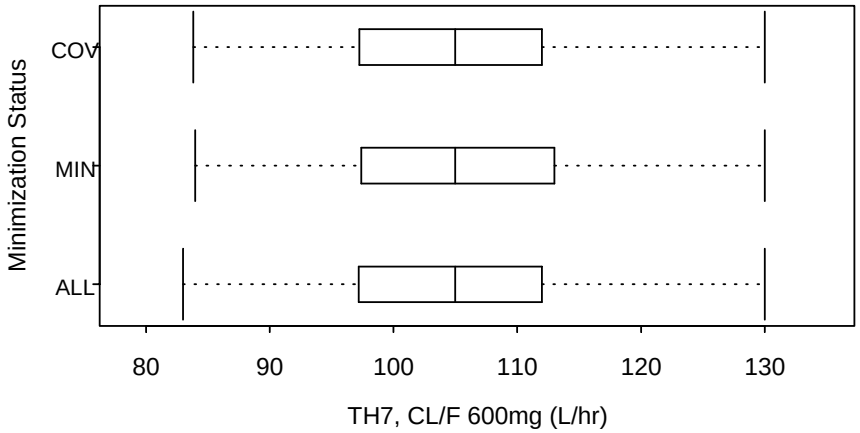

Minimization Status
COV
MIN
ALL
0.6
0.7
0.8
0.9
TH2, ALAG 1200mg 1/hr

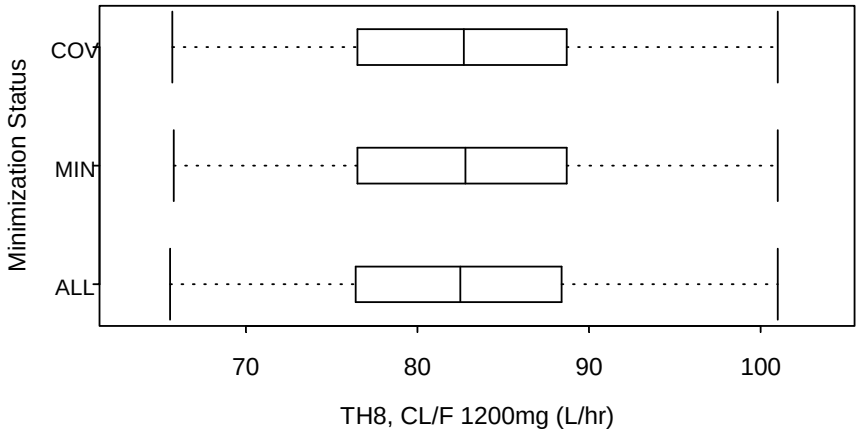

Minimization Status
COV
MIN
ALL
5
10
15
TH3, KA 600mg 1/hr

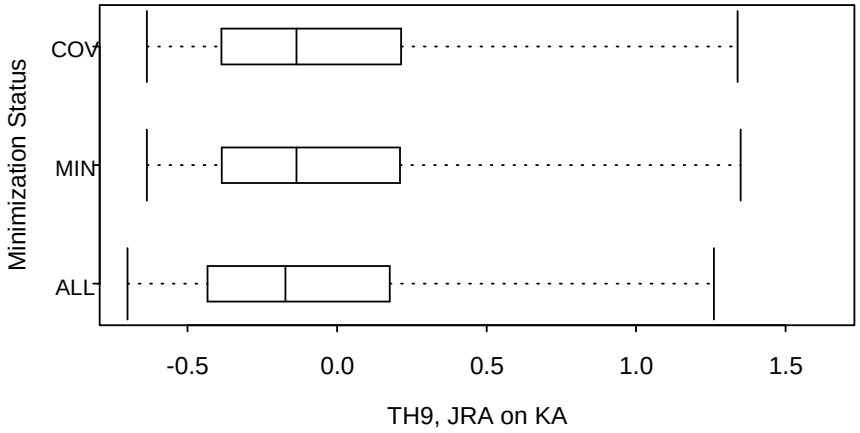

Minimization Status
COV
MIN
ALL
1
2
3
4
TH4, KA 1200mg 1/hr

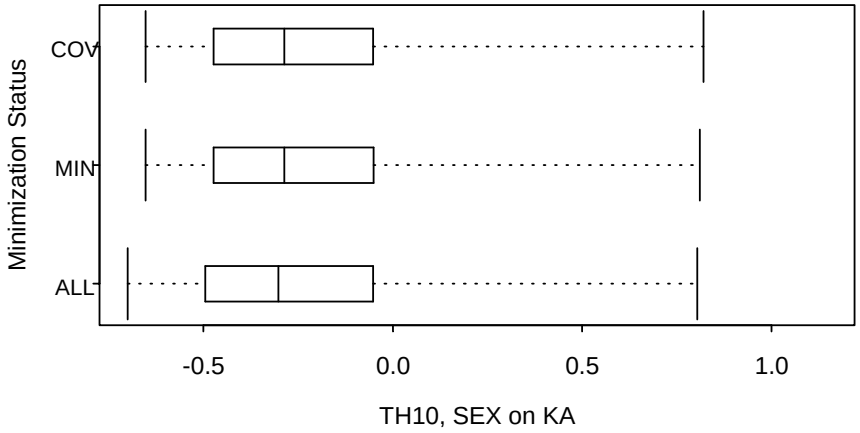

Minimization Status
COV
MIN
ALL
1400
1600
1800
2000
2200
2400
2600
TH5, V/F 600mg (L)

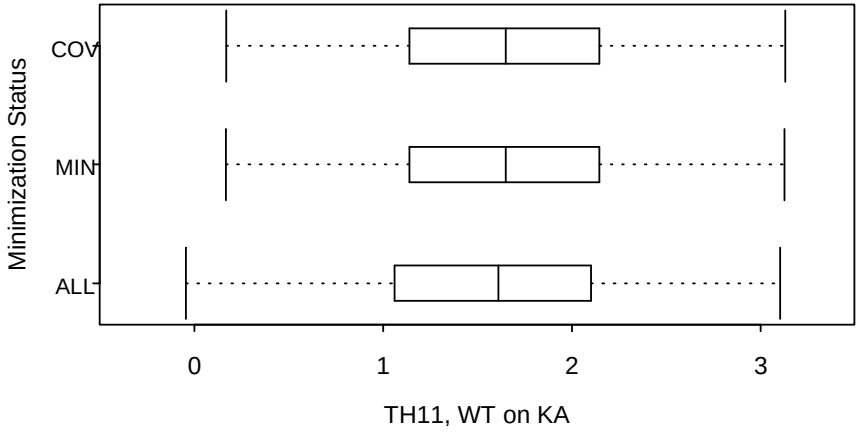

Minimization Status
COV
MIN
ALL
900
1000
1100
1200
1300
TH6, V/F 1200mg (L)

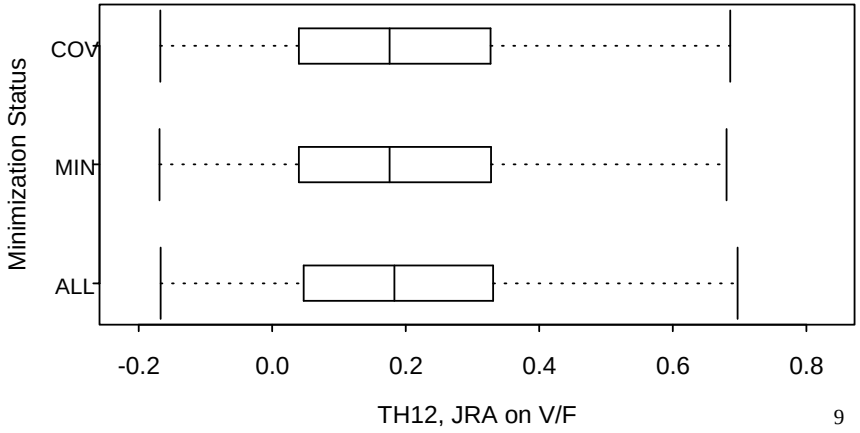

Minimization Status
COV
MIN
ALL
80
90
100
110
120
130
TH7, CL/F 600mg (L/hr)

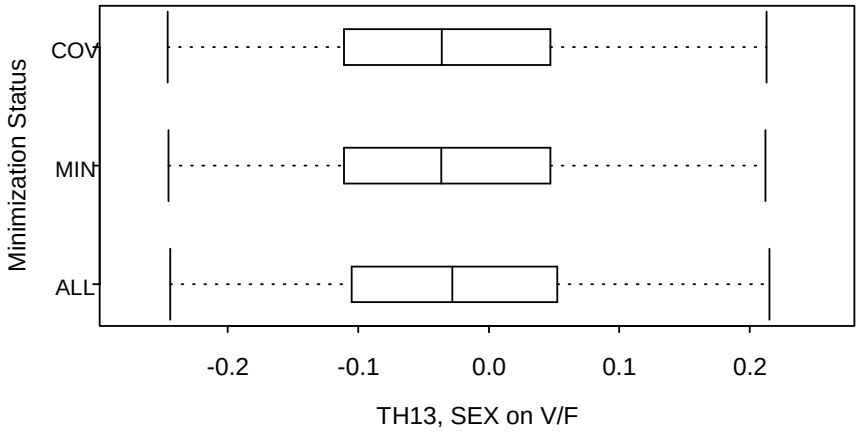

Minimization Status
COV
MIN
ALL
70
80
90
100
TH8, CL/F 1200mg (L/hr)

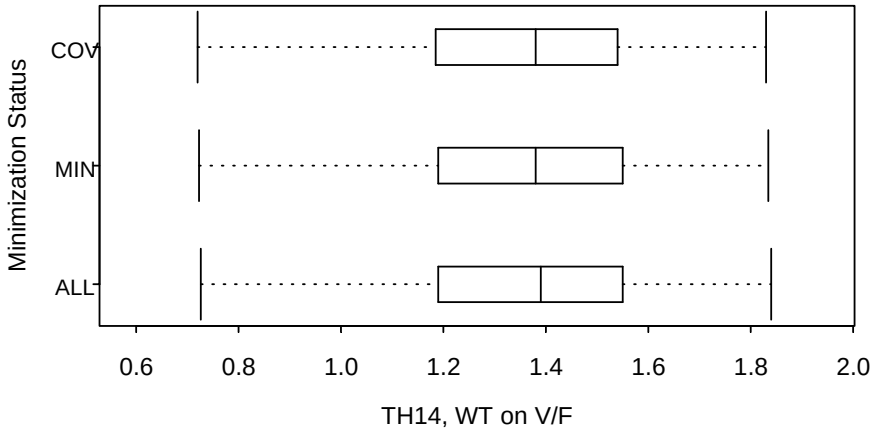

Minimization Status
COV
MIN
ALL
-0.5
0.0
0.5
1.0
1.5
TH9, JRA on KA

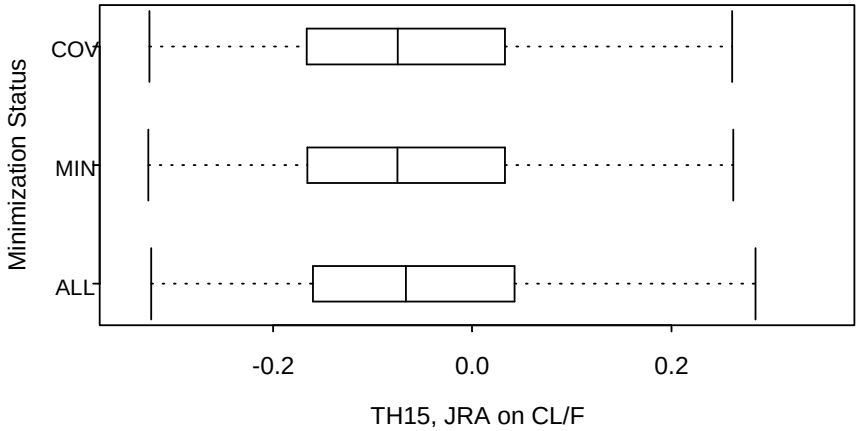

Minimization Status
COV
MIN
ALL
-0.5
0.0
0.5
1.0
TH10, SEX on KA

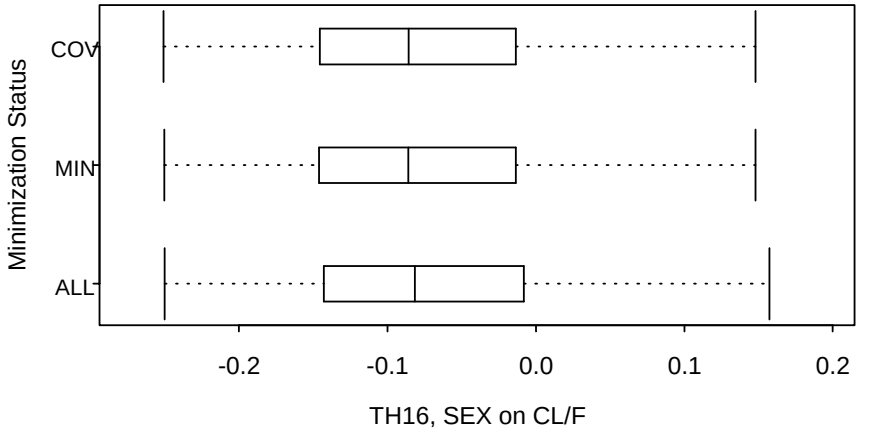

Minimization Status
COV
MIN
ALL
0
1
2
3
TH11, WT on KA

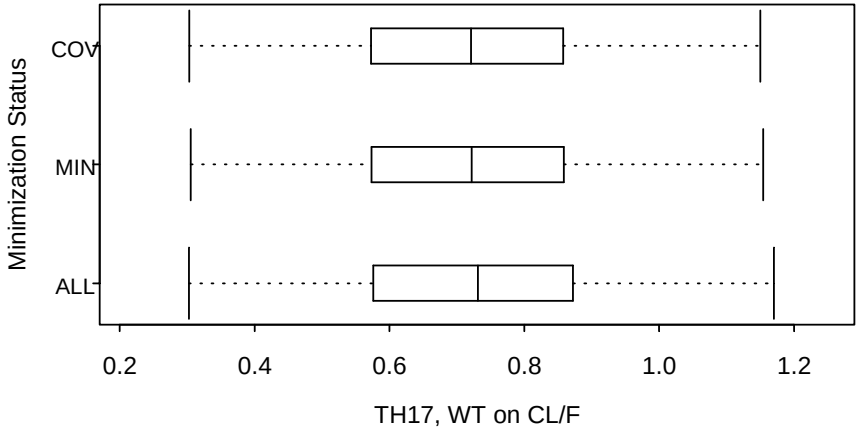

Minimization Status
COV
MIN
ALL
-0.2
0.0
0.2
0.4
0.6
0.8
TH12, JRA on V/F

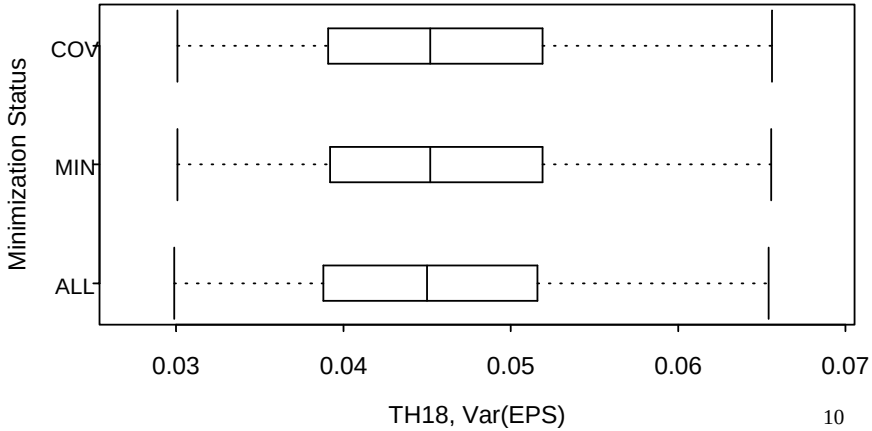

Minimization Status
COV
MIN
ALL
-0.2
-0.1
0.0
0.1
0.2
TH13, SEX on V/F

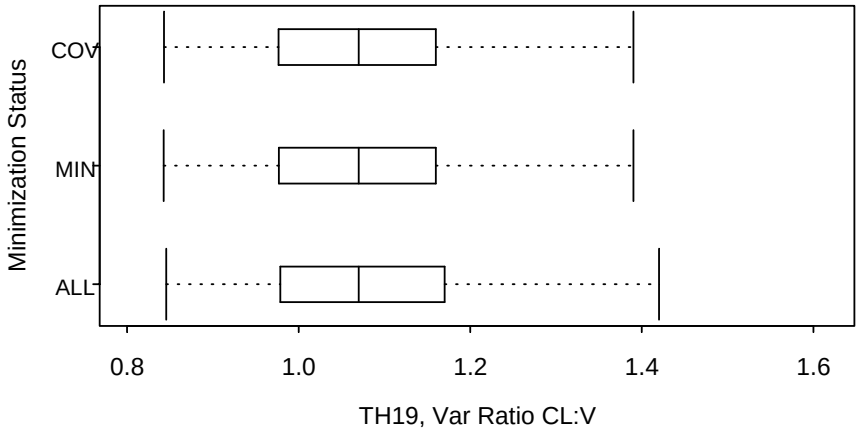

Minimization Status
COV
MIN
ALL
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
TH14, WT on V/F

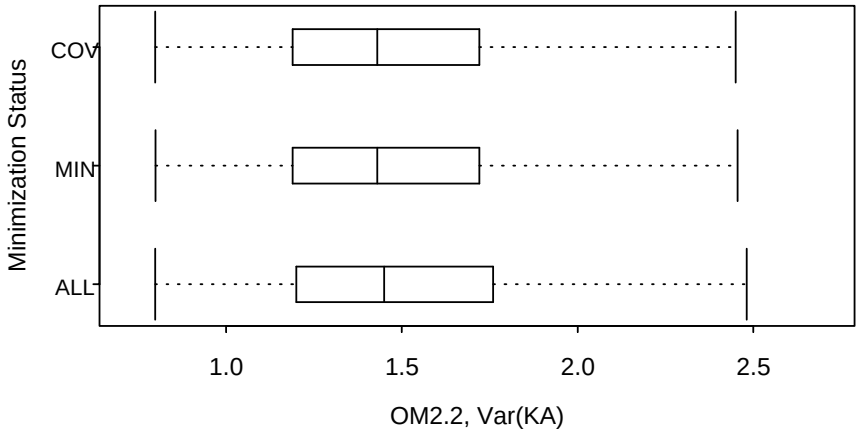

Minimization Status
COV
MIN
ALL
-0.2
0.0
0.2
TH15, JRA on CL/F


Minimization Status
COV
MIN
ALL
-0.2
-0.1
0.0
0.1
0.2
TH16, SEX on CL/F


Minimization Status
COV
MIN
ALL
0.2
0.4
0.6
0.8
1.0
1.2
TH17, WT on CL/F


Minimization Status
COV
MIN
ALL
0.03
0.04
0.05
0.06
0.07
TH18, Var(EPS)


Minimization Status
COV
MIN
ALL
0.8
1.0
1.2
1.4
1.6
TH19, Var Ratio CL:V


Minimization Status
COV
MIN
ALL
1.0
1.5
2.0
2.5
OM2.2, Var(KA)

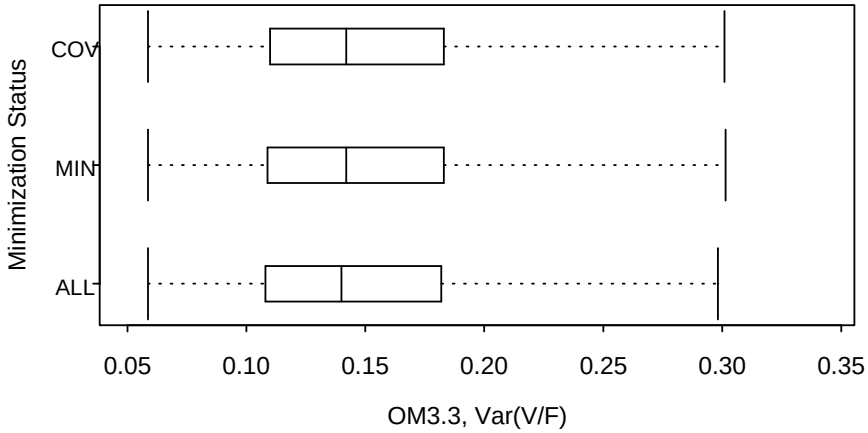

Minimization Status
COV
MIN
ALL
0.05
0.10
0.15
0.20
0.25
0.30
0.35
OM3.3, Var(V/F)

Table 1: Change in Bootstrap 95% CI as Function of Minimization Status

Average Percent Change in Confidence Interval Across All Parameters

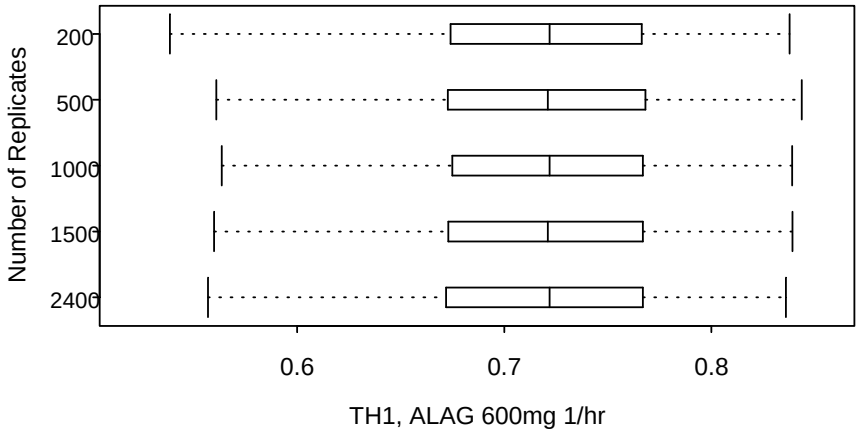
Comparison of Minimization Status	% Change in CI Lower Bound	% Change in CI Upper Bound
COV -> MIN	0.3	0.3
MIN -> ALL	1.5	3.0

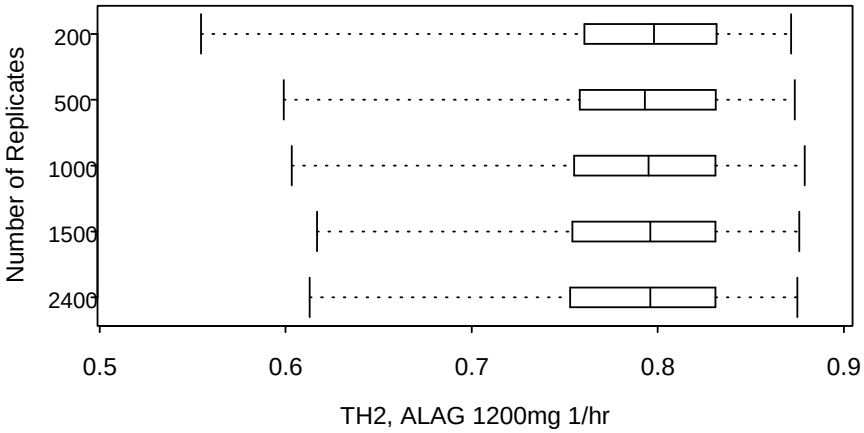
Maximum Percent Change in Confidence Interval Across All Parameters

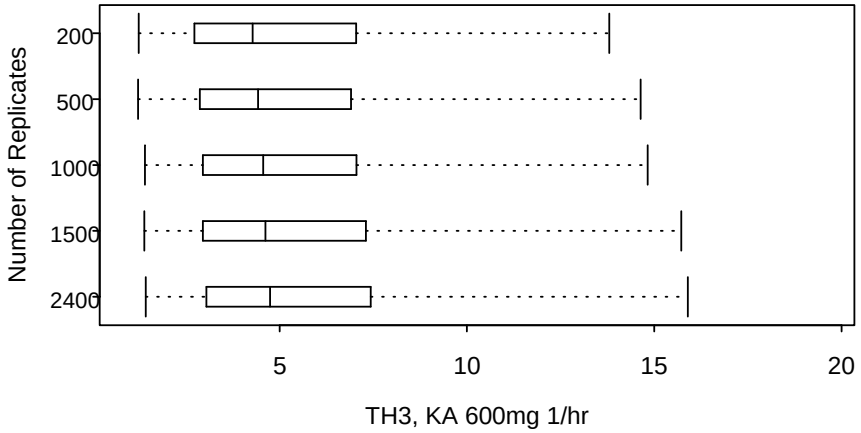
Comparison of Minimization Status	% Change in CI Lower Bound	% Change in CI Upper Bound
COV -> MIN	0.7	1.4
MIN -> ALL	10.2	15.2

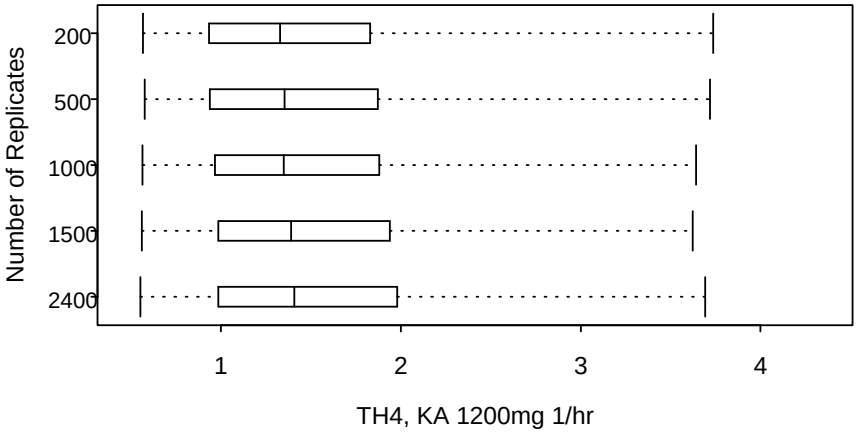
Figure 2: Effect of Number of Replicates on BS Parameter Distributions

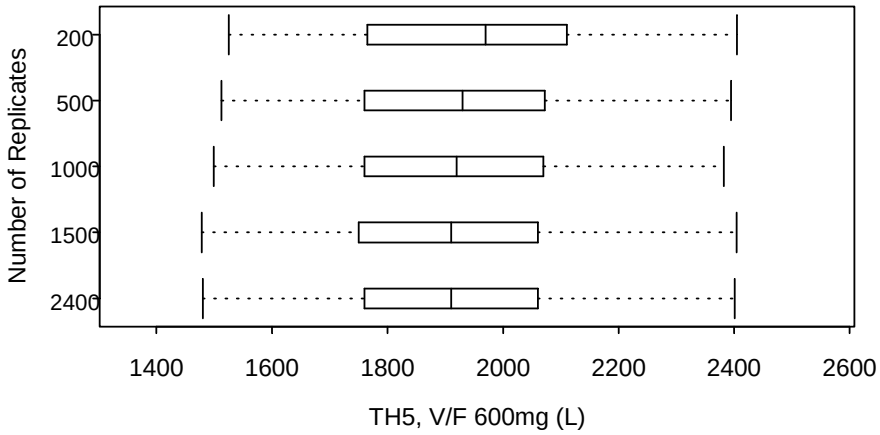
- Box plots representing resulting BS parameter distributions are presented for each model parameter, categorized by number of replicates (200, 500, 1000, 1500 or 2400).
- Whiskers indicate the 95% CI, the box indicates the inter-quartile range, and the vertical line in the box indicates the median of the parameter distribution

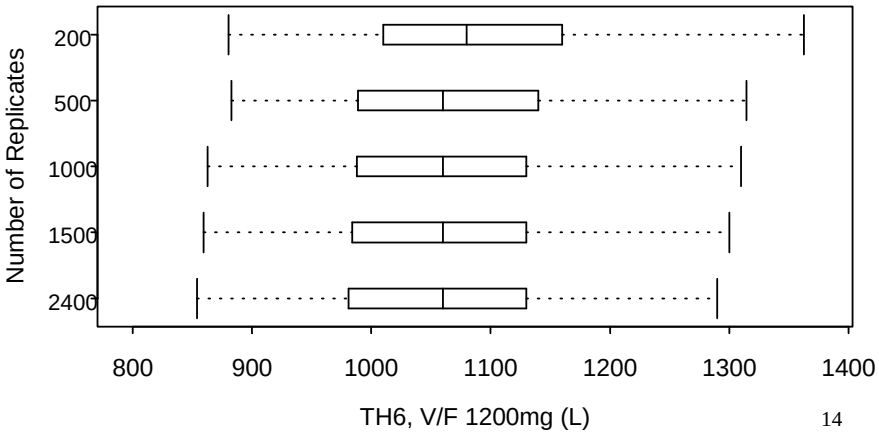

Number of Replicates
200
500
1000
1500
2400
0.6
0.7
0.8
TH1, ALAG 600mg 1/hr

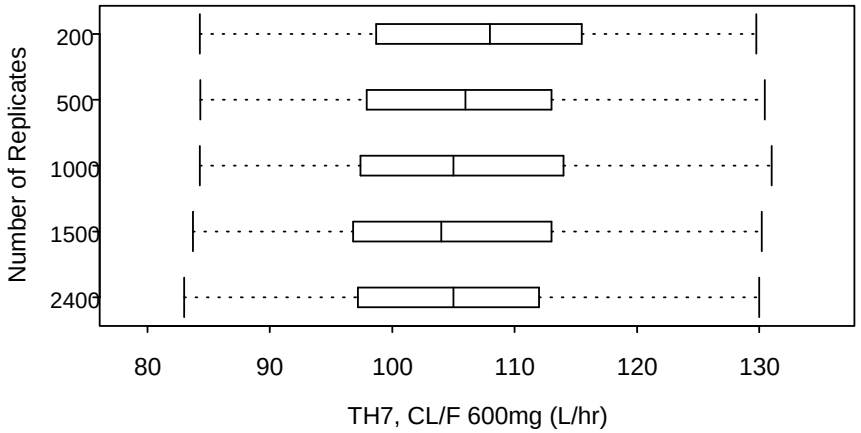

Number of Replicates
200
500
1000
1500
2400
0.5
0.6
0.7
0.8
0.9
TH2, ALAG 1200mg 1/hr

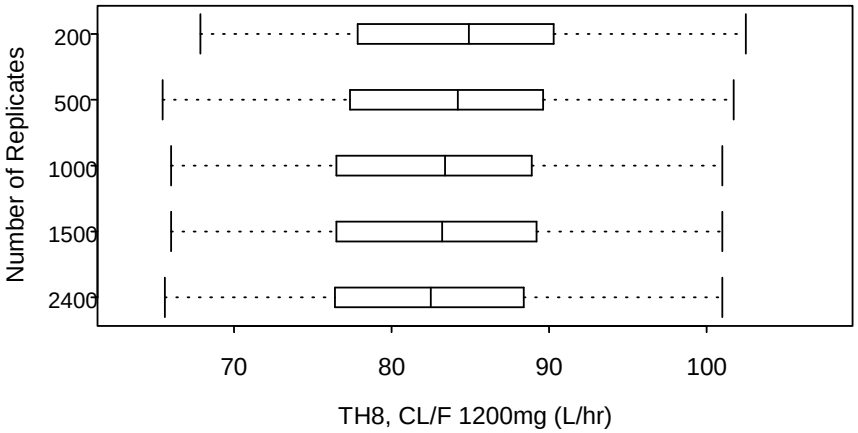

Number of Replicates
200
500
1000
1500
2400
5
10
15
20
TH3, KA 600mg 1/hr

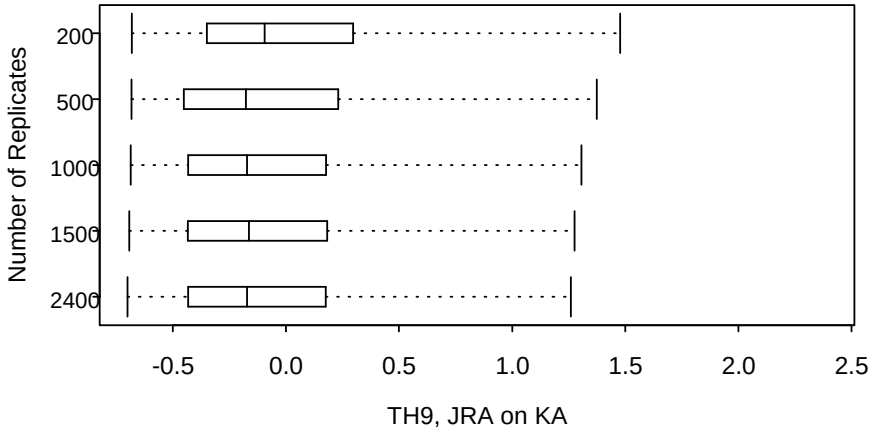

Number of Replicates
200
500
1000
1500
2400
1
2
3
4
TH4, KA 1200mg 1/hr

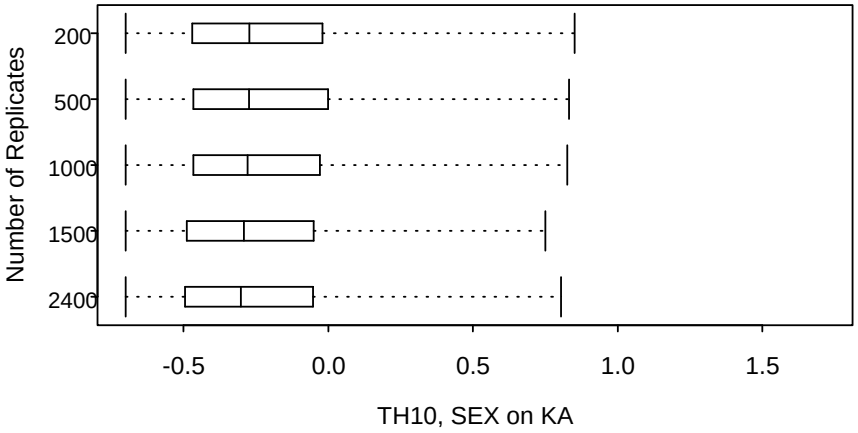

Number of Replicates
200
500
1000
1500
2400
1400
1600
1800
2000
2200
2400
2600
TH5, V/F 600mg (L)

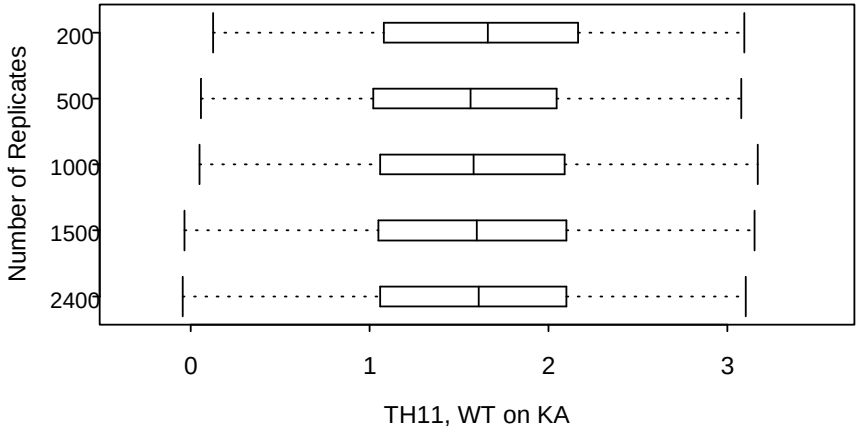

Number of Replicates
200
500
1000
1500
2400
800
900
1000
1100
1200
1300
1400
TH6, V/F 1200mg (L)

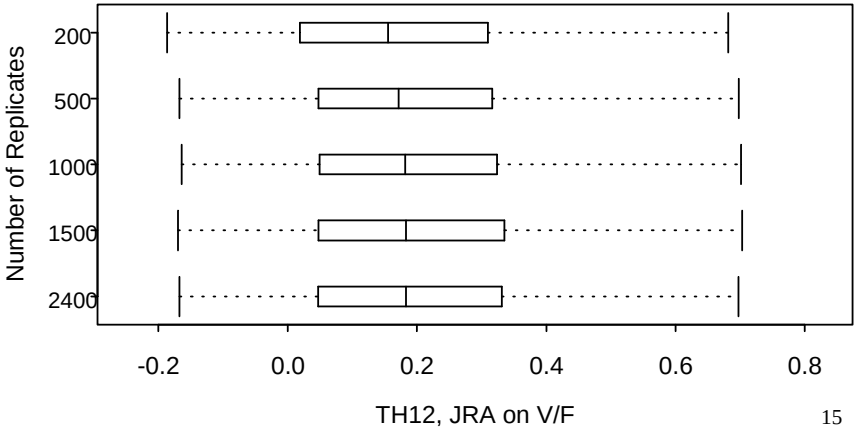

Number of Replicates
200
500
1000
1500
2400
80
90
100
110
120
130
TH7, CL/F 600mg (L/hr)

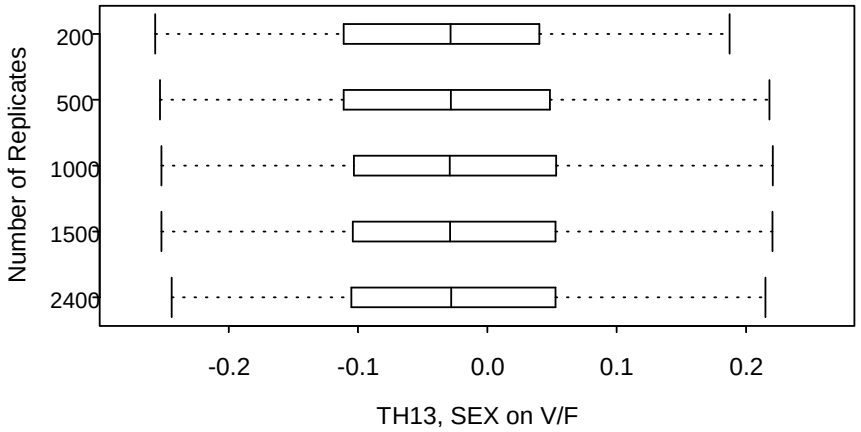

Number of Replicates
200
500
1000
1500
2400
70
80
90
100
TH8, CL/F 1200mg (L/hr)

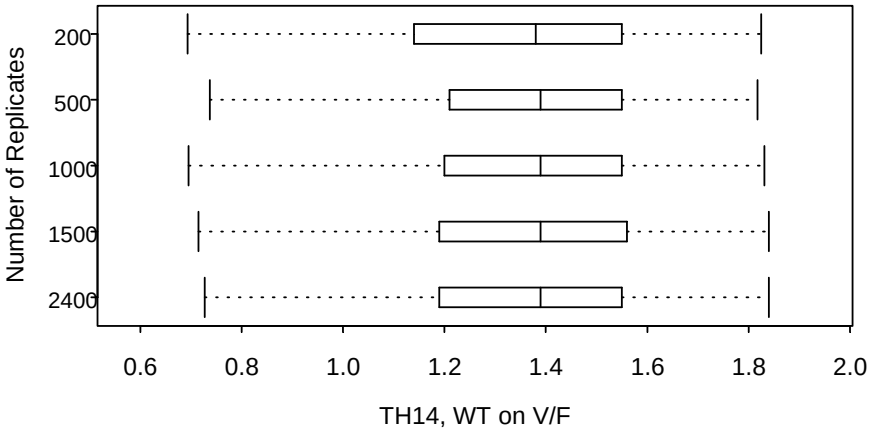

Number of Replicates
200
500
1000
1500
2400
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
TH9, JRA on KA

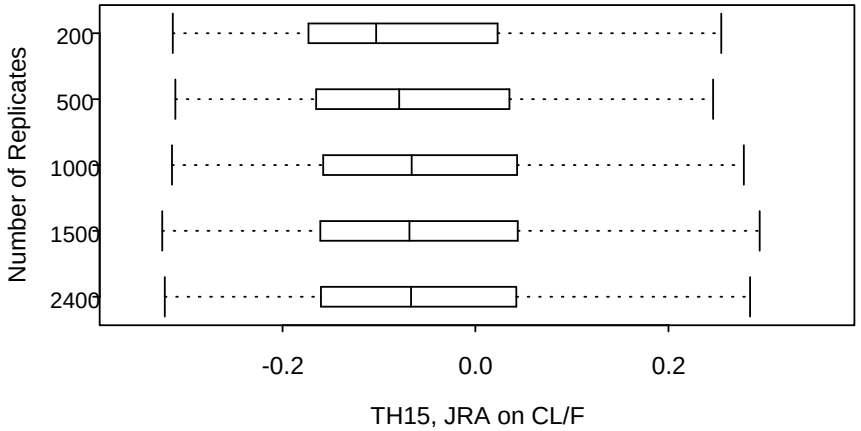

Number of Replicates
200
500
1000
1500
2400
-0.5
0.0
0.5
1.0
1.5
TH10, SEX on KA

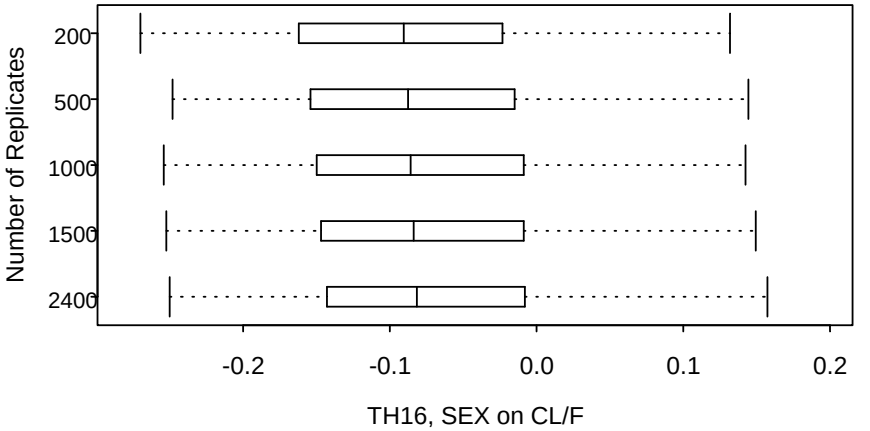

Number of Replicates
200
500
1000
1500
2400
0
1
2
3
TH11, WT on KA

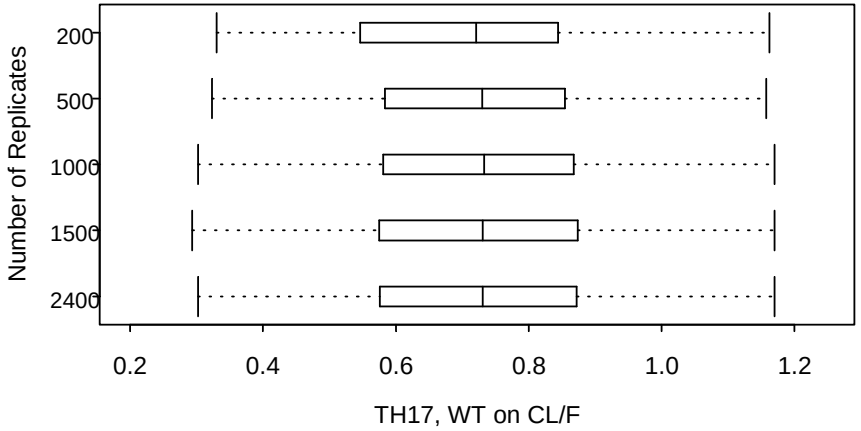

Number of Replicates
200
500
1000
1500
2400
-0.2
0.0
0.2
0.4
0.6
0.8
TH12, JRA on V/F

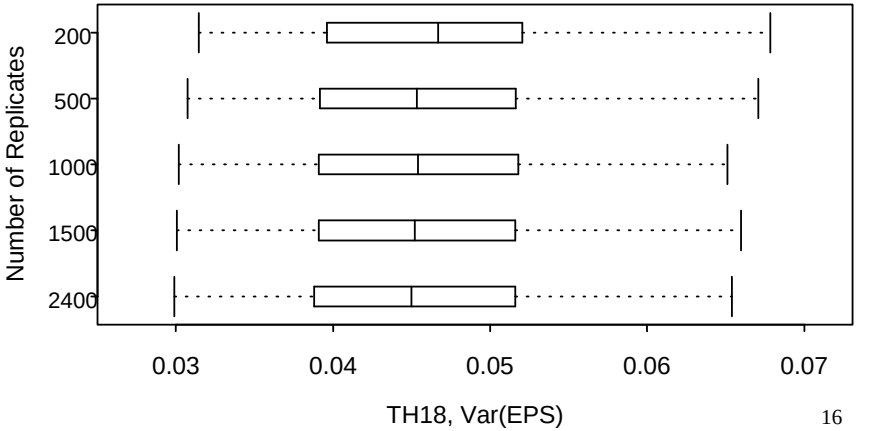

Number of Replicates
200
500
1000
1500
2400
-0.2
-0.1
0.0
0.1
0.2
TH13, SEX on V/F

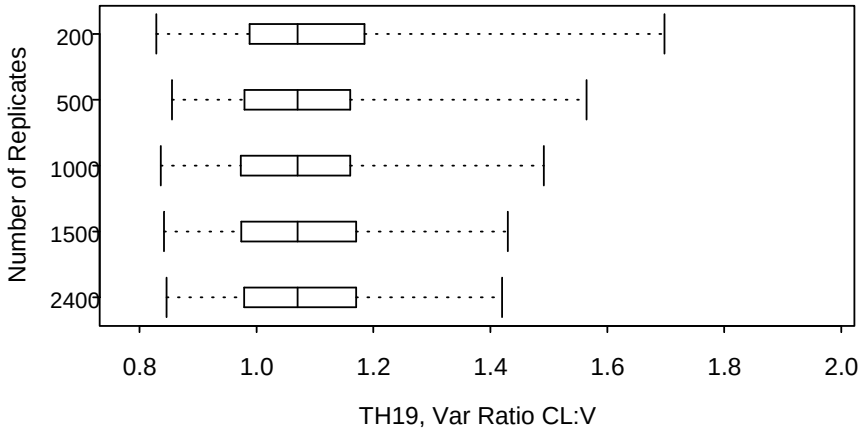

Number of Replicates
200
500
1000
1500
2400
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
TH14, WT on V/F

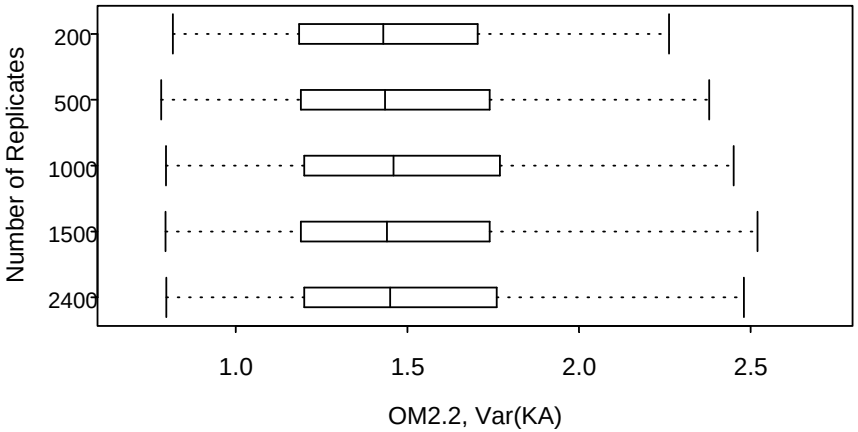

Number of Replicates
200
500
1000
1500
2400
-0.2
0.0
0.2
TH15, JRA on CL/F


Number of Replicates
200
500
1000
1500
2400
-0.2
-0.1
0.0
0.1
0.2
TH16, SEX on CL/F


Number of Replicates
200
500
1000
1500
2400
0.2
0.4
0.6
0.8
1.0
1.2
TH17, WT on CL/F


Number of Replicates
200
500
1000
1500
2400
0.03
0.04
0.05
0.06
0.07
TH18, Var(EPS)


Number of Replicates
200
500
1000
1500
2400
0.8
1.0
1.2
1.4
1.6
1.8
2.0
TH19, Var Ratio CL:V


Number of Replicates
200
500
1000
1500
2400
1.0
1.5
2.0
2.5
OM2.2, Var(KA)

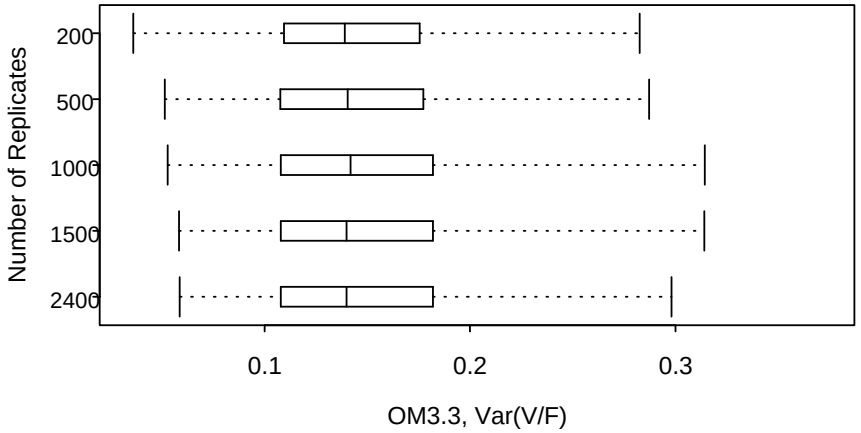

Number of Replicates
200
500
1000
1500
2400
0.1
0.2
0.3
OM3.3, Var(V/F)

Table 2: Change in Bootstrap 95% CI with Increased Number of Replicates

Average Percent Change in Confidence Interval Across All Parameters

Increase in Number of Replicates	% Change in CI Lower Bound	% Change in CI Upper Bound
200 -> 500	5.2	3.5
500 -> 1000	2.4	2.5
1000 -> 1500	1.7	2.1
1500 -> 2400	1.1	1.7

Maximum Percent Change in Confidence Interval Across All Parameters

Increase in Number of Replicates	% Change in CI Lower Bound	% Change in CI Upper Bound
200 -> 500	42.7	16.0
500 -> 1000	15.6	13.0
1000 -> 1500	10.4	9.3
1500 -> 2400	3.4	7.3

Conclusions/Discussion: Minimization Status

- Minimization status had minimal impact on the resulting BS parameter distributions
- Across all parameters the average change in BS CIs was no more than 3% (Table 1, top)
- The most sensitive parameter resulted in 10.2% and 15.2 % changes in the upper and lower CI bounds, respectively (Table 1, bottom).
- For those BS parameter distributions that were sensitive to minimization status, the use of ALL replicates provided the broadest BS distribution
- Although these findings are specific to this case, it is likely that the use of ALL replicates will generally provide the most complete (and conservative) reflection of the uncertainty in parameter estimates

Conclusions/Discussion: Number of BS Replicates

- BS parameter distributions were sensitive to the number of BS replicates (Figure 2)
- Across all parameters, the average change in BS CIs was no more than 5.2% (Table 2, top), while the most sensitive parameter resulted in up to 42.7% and 16 % changes in the upper and lower CI bounds, respectively (Table 2, bottom)
- For most parameters, BS CIs were stable within 1000 replicates and minimal change was evident in any parameter when at least 1500 replicates were used.
- These findings are specific to this case and the required number of BS replicates should be investigated for each problem, using similar methods.
- A general estimate of 1000 replicates may be a useful starting point.

References

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