Evaluating the IPPSE method for PKPD analysis

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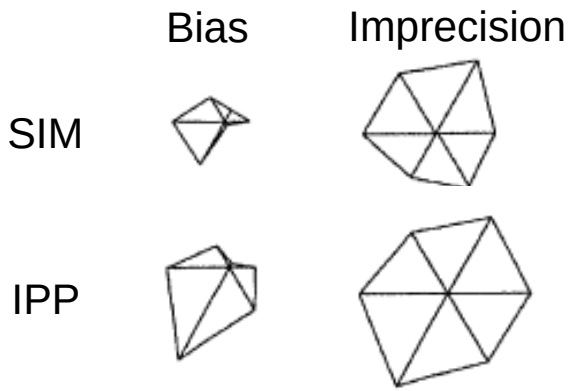
Background

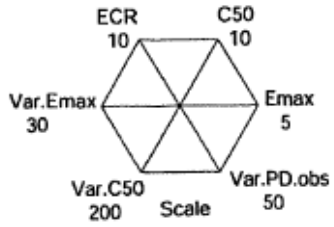
- *Simultaneous PKPD analysis*
  - Gold standard

SIM

- *Sequential PKPD analysis*
  - Common: ↘ run time and ↗ stability
  - Condition on individual PK parameters
  - But ↗ the bias and imprecision

IPP





L. Zhang, S.L. Beal & L.B. Sheiner, JPKPD 2003; 30: 387-404

Background

- *Simultaneous PKPD analysis*
  - Gold standard

- *Sequential PKPD analysis*
  - Common: ↘ run time and ↗ stability
  - Conditioned on individual PK parameters
  - But ↗ the bias and imprecision

IPPSE method

  - *Sequential*
  - *Do not assume ind. PK parameters are exactly known*

IPPSE method

- *PK step → SE(individual PK parameters)*
  - Generated by NONMEM7
  - Available in NONMEM VI via *e.g.* PsN
- *PD step*

```
$INPUT ID TIME DV AMT ICL IV SECL SEV

$PK   CL= ICL*EXP(ETA(3)*SECL)
      V  = IV*EXP(ETA(4)*SEV)
      S1= V

$ERROR
 BASE   = THETA(1)*EXP(ETA(1))
 SLOPE= THETA(2)*EXP(ETA(2))
 EFF    = BASE + SLOPE*F
 Y      = EFF*(1+EPS(1))
```

```
$THETA (0,1)      ;1 BASE
$THETA (0, 9)     ;2 SLOPE
$OMEGA .1         ;1 IIV BASE
$OMEGA .1         ;2 IIV SLOPE
$OMEGA 1 FIX      ;3 IIV CL
$OMEGA 1 FIX      ;4 IIV V
$SIGMA  .2        ;1 RES ERROR
```

Method

- *Simulated datasets, N=200*
  - Various study designs

Subject number	[10 ; 50]	LHS, Uniform distribution
Average No of PK observations by subject	[2 ; 7]	LHS, Uniform distribution
Average No of PD observations by subject	[2 ; 7]	LHS, Uniform distribution
Sampling time	[0 ; 10]	Sampling scheme

  - One-cpt PK model, direct Emax PD model

LHS= latin hypercube sampling

Clearance (CL)	3.46	Fixed, scale factor
Volume (V)	10	Fixed, scale factor
Emax	10	Fixed, scale factor
C50	[1 ; 5]	LHS, Uniform distribution
ω^2 (CL, V, C50)	[0.01 ; 0.09]	LHS, Uniform distribution
σ^2 prop (Cp, E)	[0.01 ; 0.09]	LHS, Uniform distribution
σ^2 add (Cp, E)	[0.04 ; 0.25]	LHS, Uniform distribution

Method

- *Estimation*
  - FOCE I method in NONMEM7

- *Performances*
  - Signed and absolute errors of the parameter estimates

$$\text{Signed error} = \frac{\text{ParTrue} - \text{ParEst}}{\text{ParTrue}}$$

$$\text{Absolute error} = \left| \text{Signed error} \right|$$

Median/Mean across replicates

Bias

Imprecision

  - Estimation time
  - Estimation status

Imprecision (%)

	Median			Mean		
	IPP	IPPSE	SIM	IPP	IPPSE	SIM
Emax	3.16	2.88	2.81	3.81	3.75	3.74
C50	11.9	11.5	10.1	14.3	13.9	13.7
VarC50	100 (96)	85 (61)	89 (58)	198 (212)	120 (126)	118 (124)

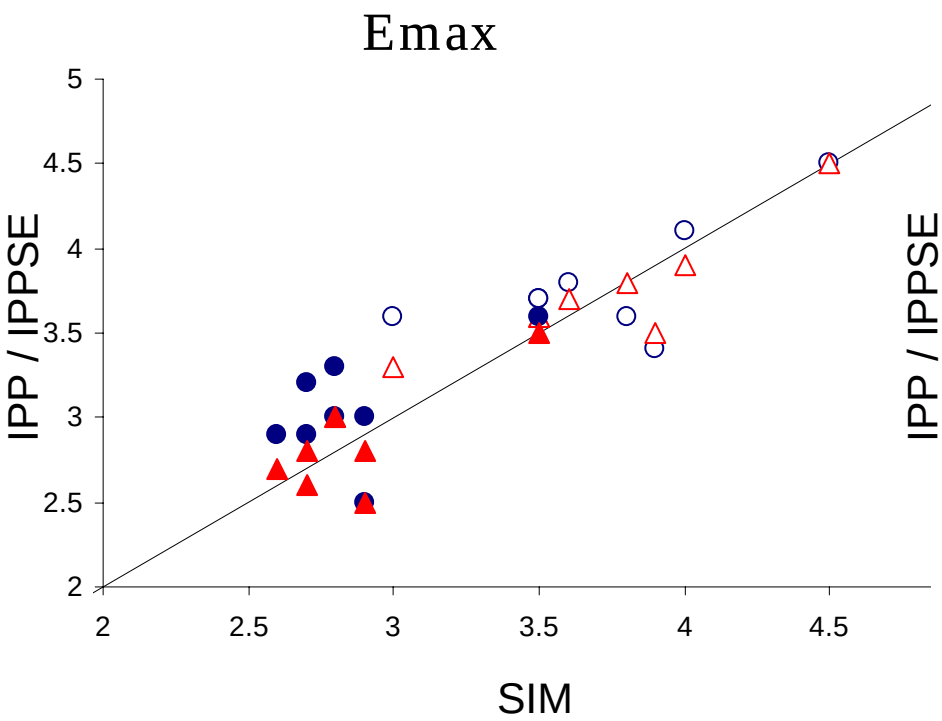
In parenthesis: calculation without the runs for which IIV was not estimated (lower boundary, close to 0)

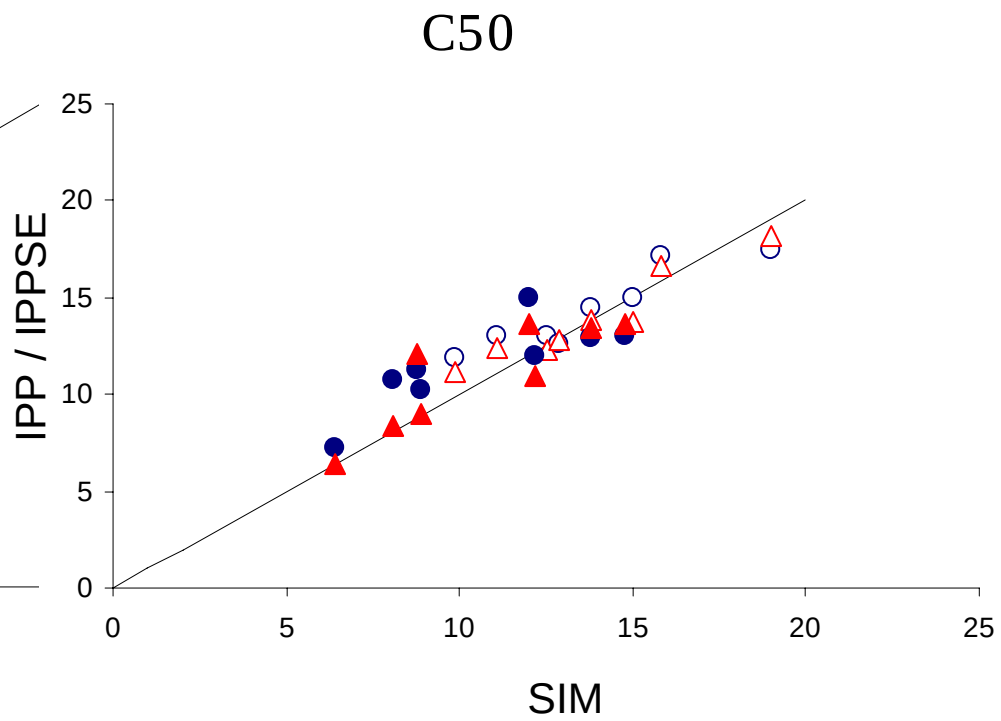
Outcome

- *All data*
- *By average number of PK and PD observations*
  - Categorized by quartiles
    - Q1 → [0 ; 3.2]
    - Q2 → [3.3 ; 4.4]
    - Q3 → [4.5 ; 5.7]
    - Q4 → [5.8 ; 7]

8 points for each mean and median value
(4 by PK observations + 4 by PD observations)

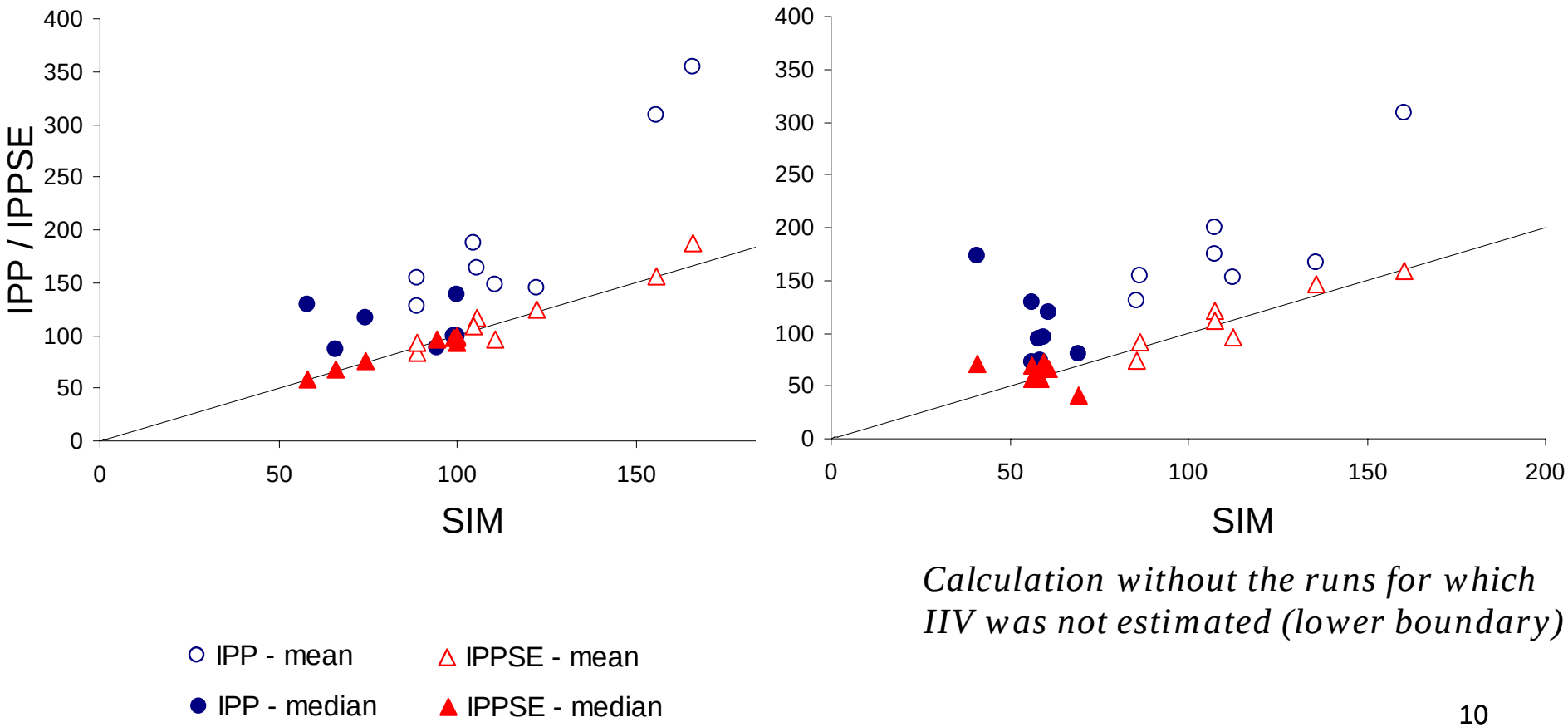
Imprecision (%)





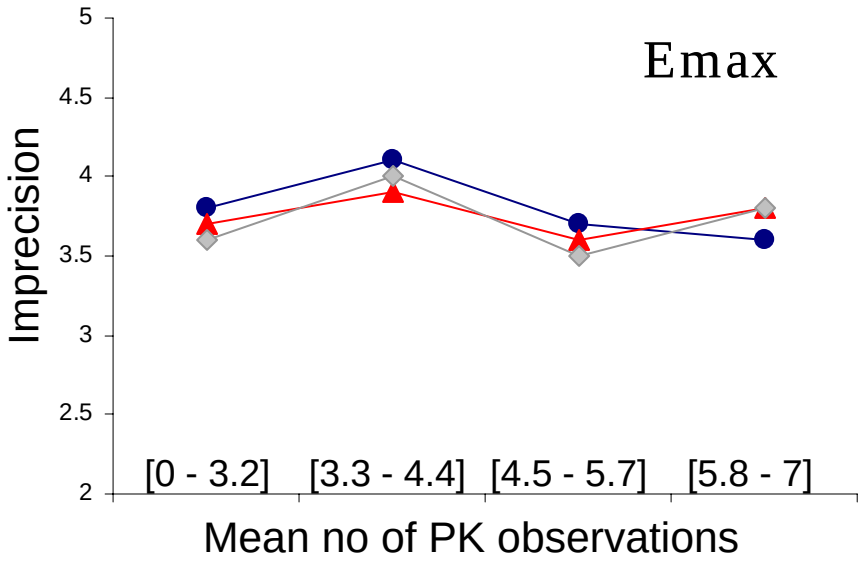
IPP - mean
IPPSE - mean
IPP - median
IPPSE - median

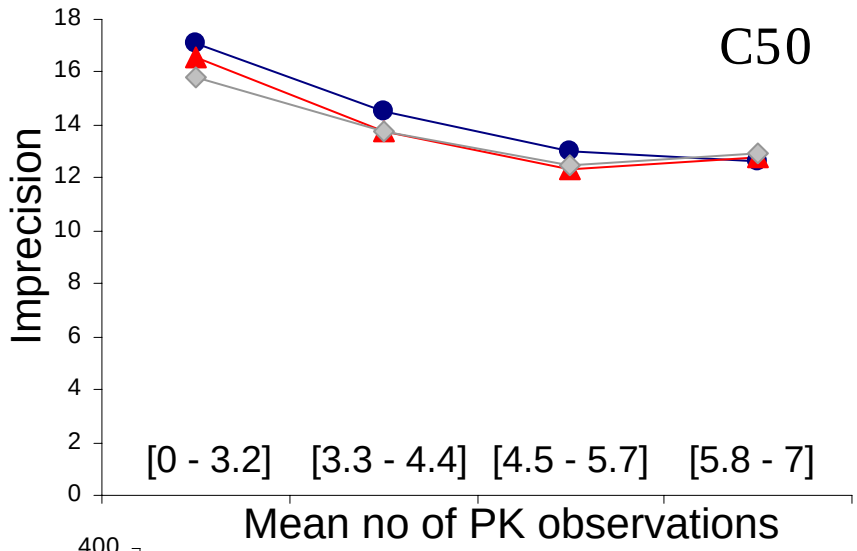
Imprecision (%)

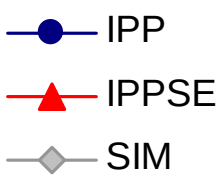


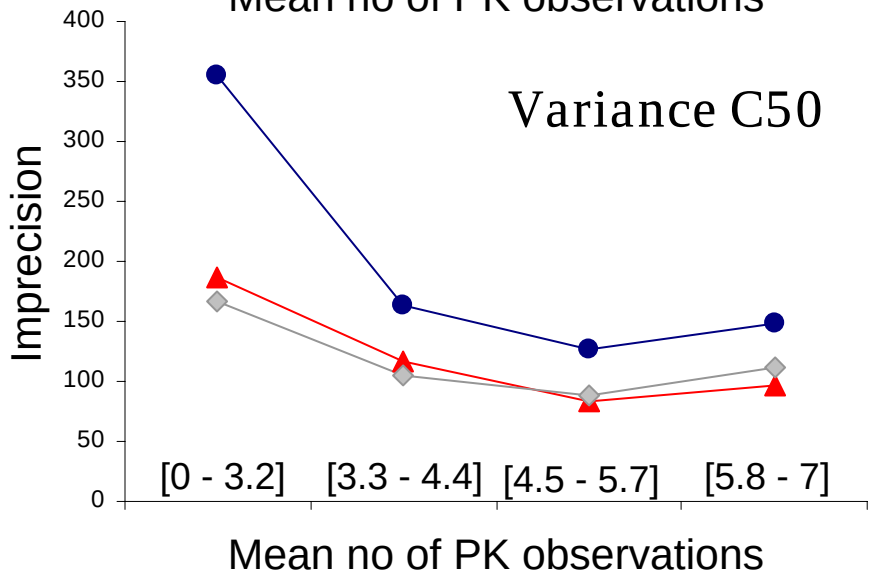
Calculation without the runs for which IIV was not estimated (lower boundary)

Imprecision by no of PK observations (mean)







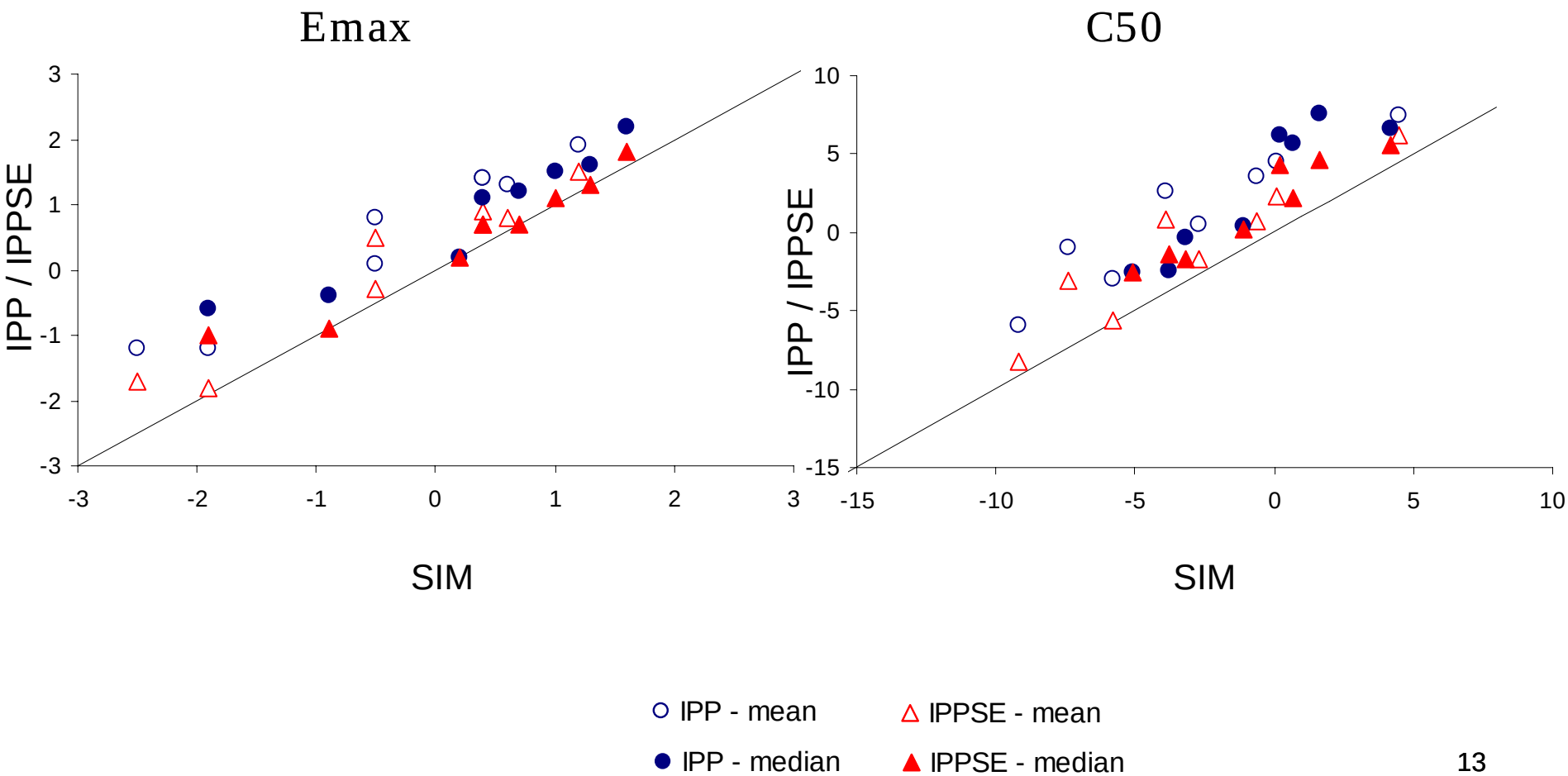


Bias (%)

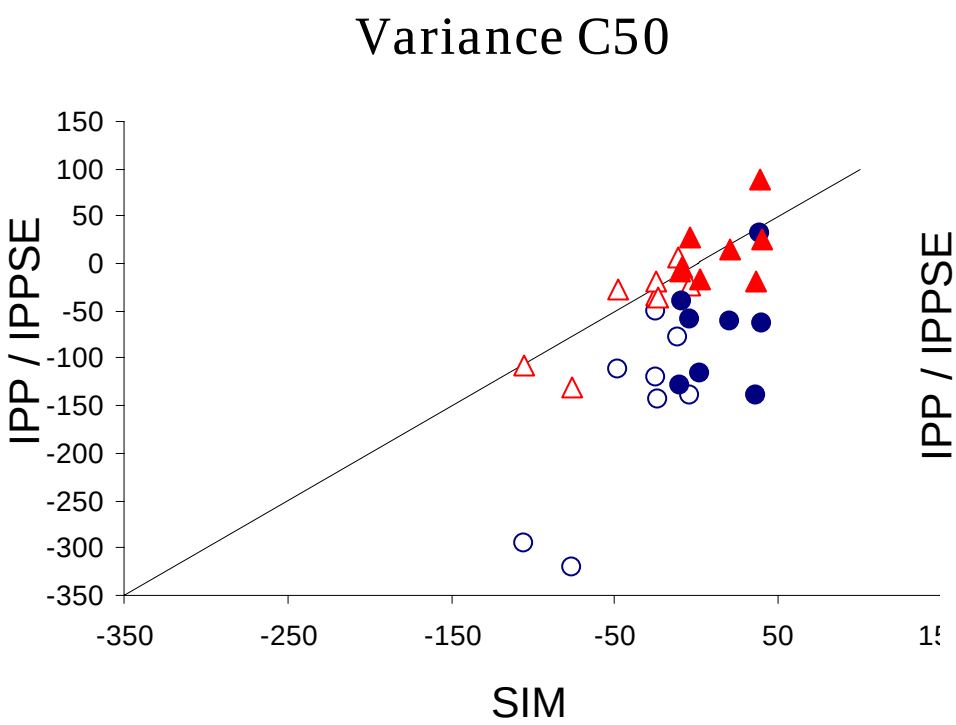
	Median			Mean		
	IPP	IPPSE	SIM	IPP	IPPSE	SIM
Emax	0.98	0.41	-0.01	0.58	0.09	-0.33
C50	3.9	1.4	0.0	1.1	-1.1	-3.1
VarC50	-71 (-94)	-0.7 (-20)	19 (-17)	-157 (-192)	-46 (-89)	-40 (-87)

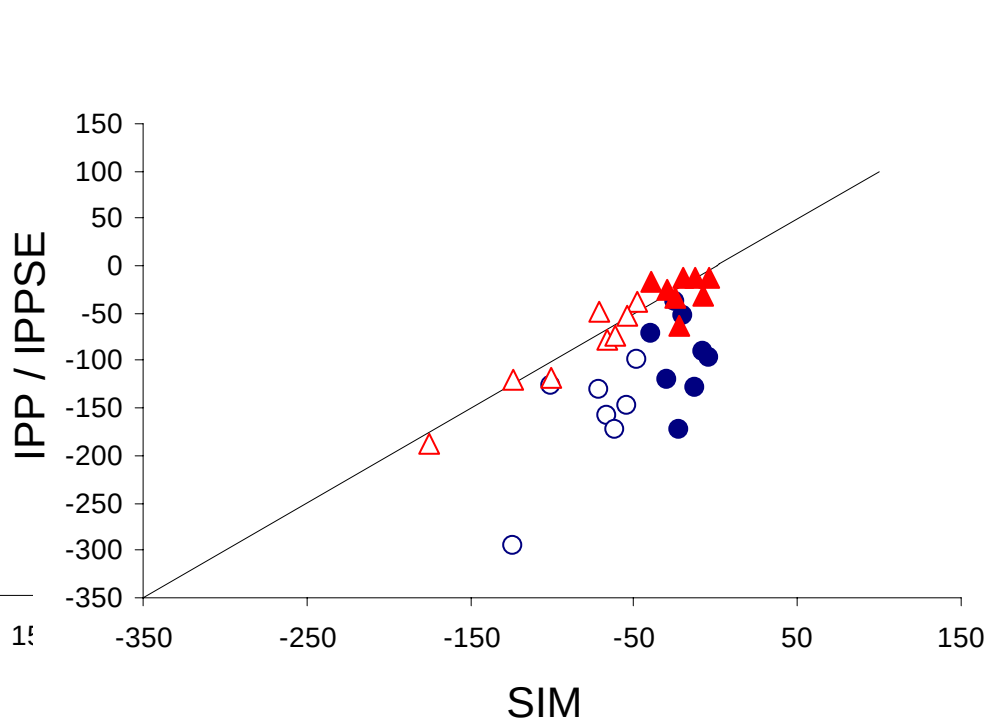
In parenthesis: calculation without the runs for which IIV was not estimated (lower boundary)

Bias (%)


Emax
IPP / IPPSE
SIM
C50
IPP / IPPSE
SIM
IPP - mean
IPPSE - mean
IPP - median
IPPSE - median

Bias (%)



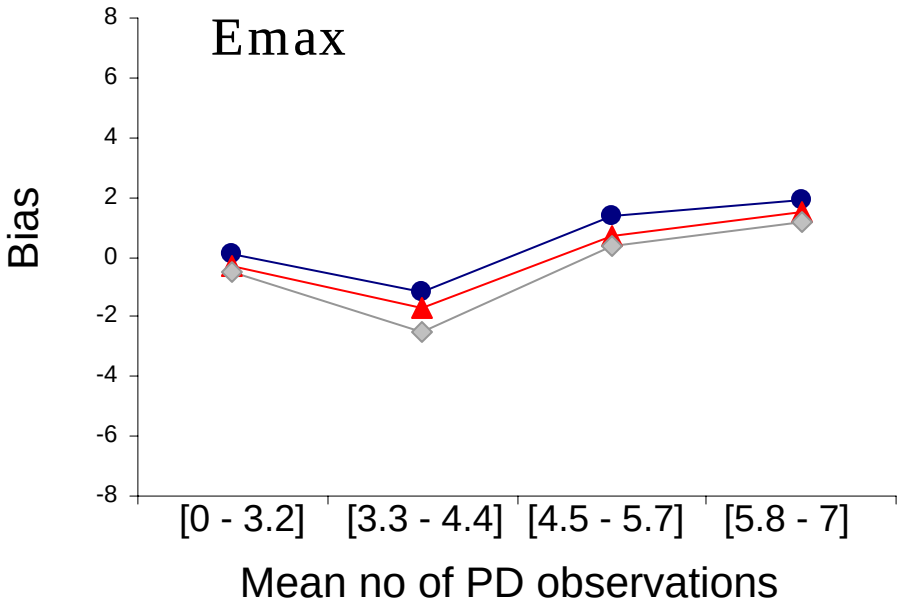


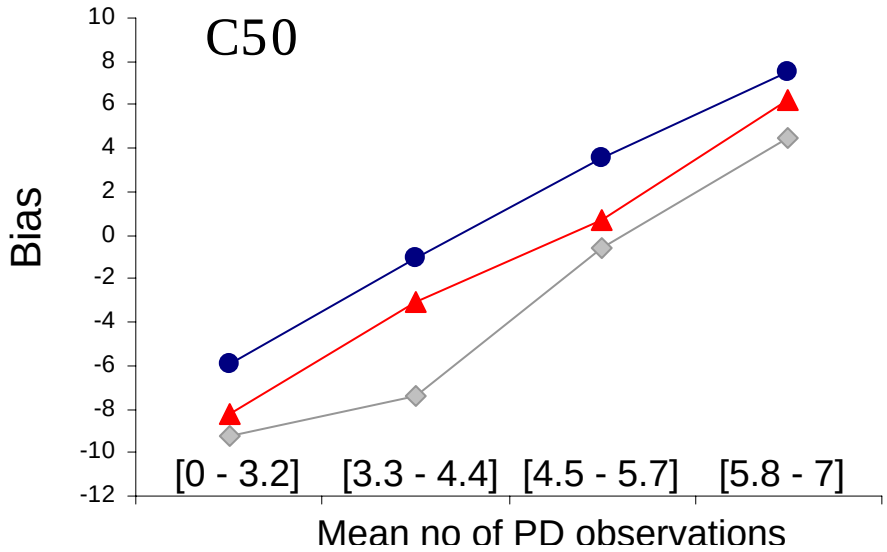
Calculation without the runs for which IIV was not estimated (lower boundary)

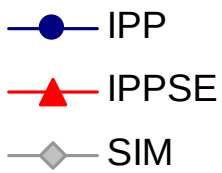
○ IPP - mean △ IPPSE - mean

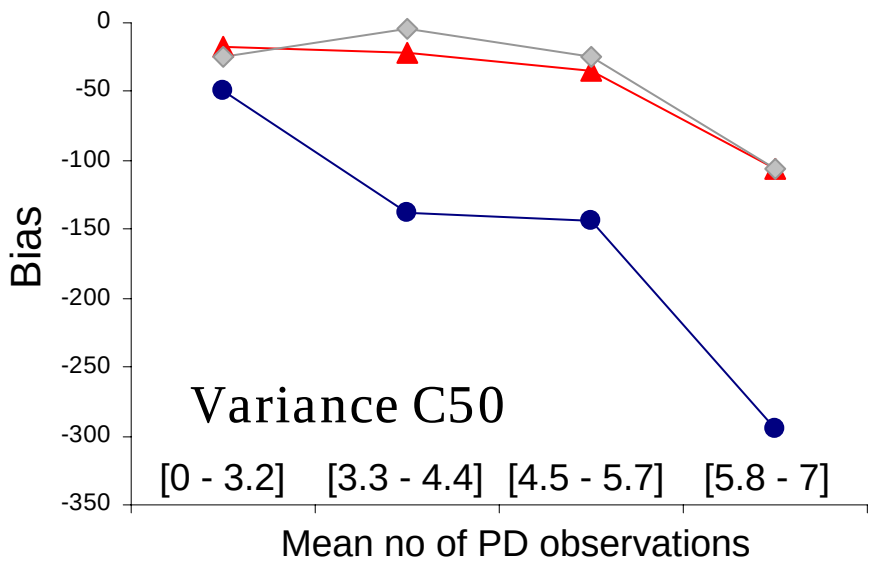
● IPP - median ▲ IPPSE - median

Bias (%) by no of PD observations (mean)



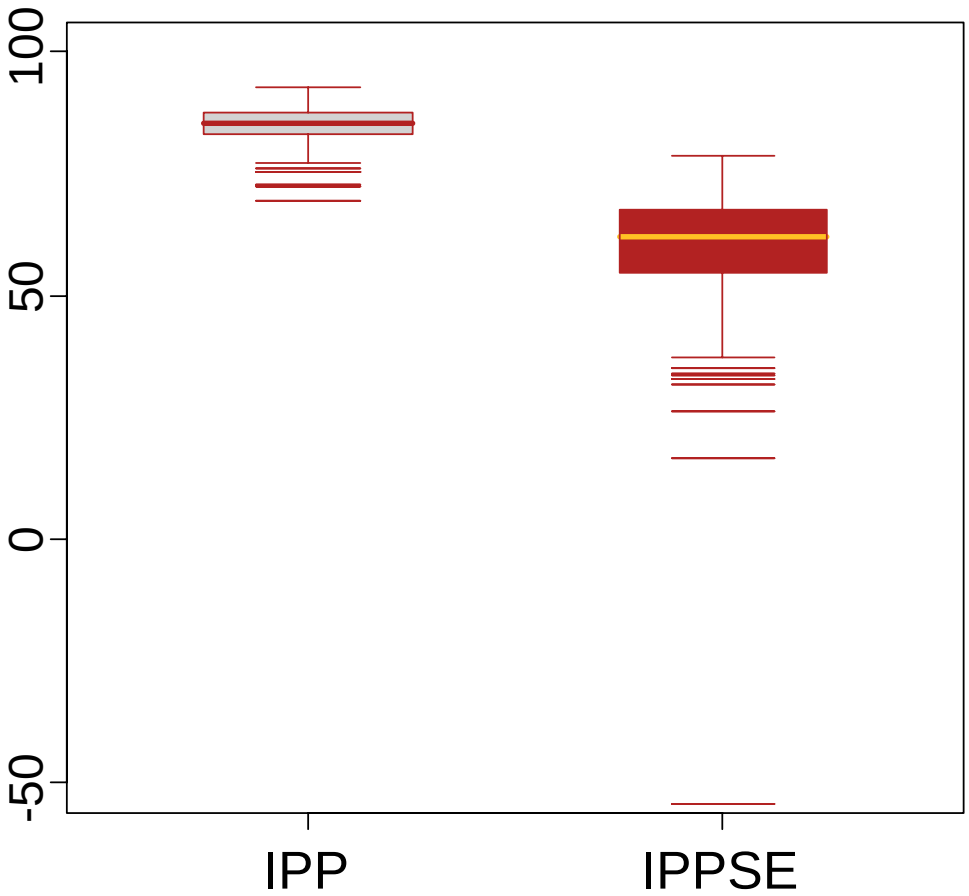






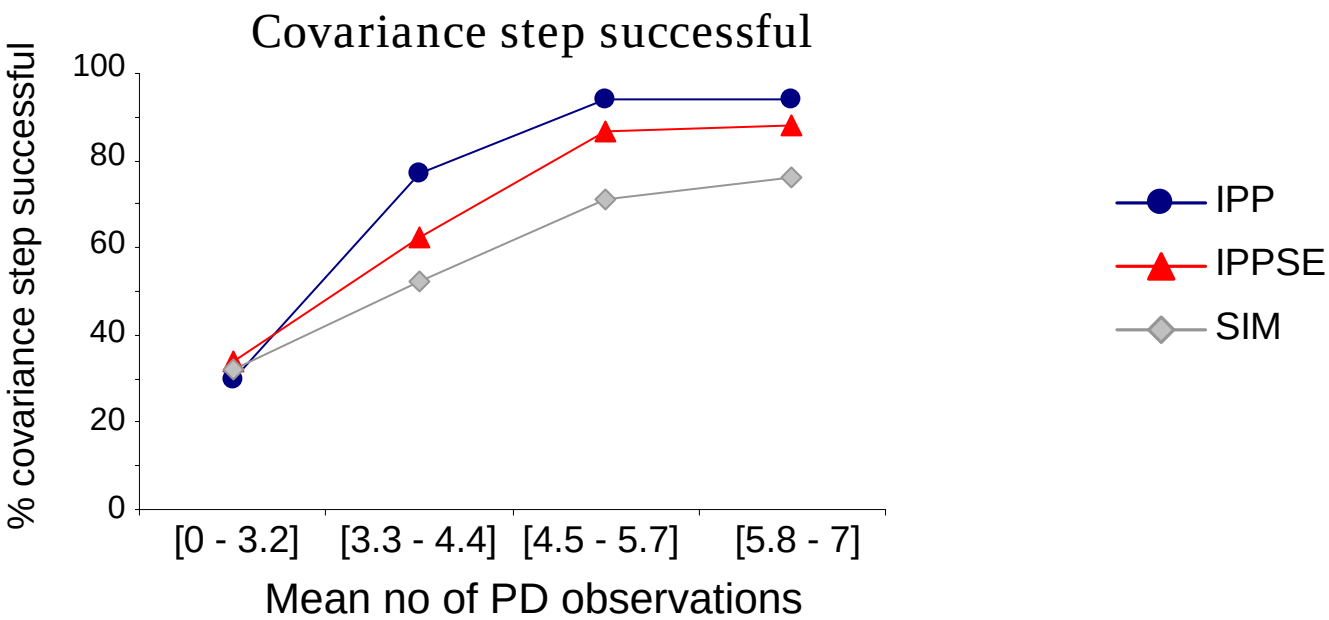
Estimation time

- % time saved using sequential methods vs. SIM



Estimation status

Criteria	IPP	IPPSE	SIM
Minimization successful	100%	100%	99.5%
Covariance step successful	74.0%	68.0%	58.0%
Estimate near boundary	24.5%	31.5%	42.0%
VarC50 not estimated	12.0%	23.0%	25.0%



Conclusion

- *IPPSE method = promising alternative for PKPD analysis*
  - Combines the advantages of the SIM and IPP methods:
    - Higher precision & lower bias than IPP
    - Shorter run time & better stability than SIM
  - Easy to implement

Acknowledgment

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