

Evaluation of NONMEM 7.3.0 and Monolix 4.2.2 by Parametric Bootstrap

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Background



- Parametric bootstrap is the gold standard method for evaluation of estimation methods
- Monolix does not provide a built in mechanism for bootstrapping
- Wings for NONMEM 731 supports parametric and non-parametric bootstrapping of NONMEM and Monolix

Methods

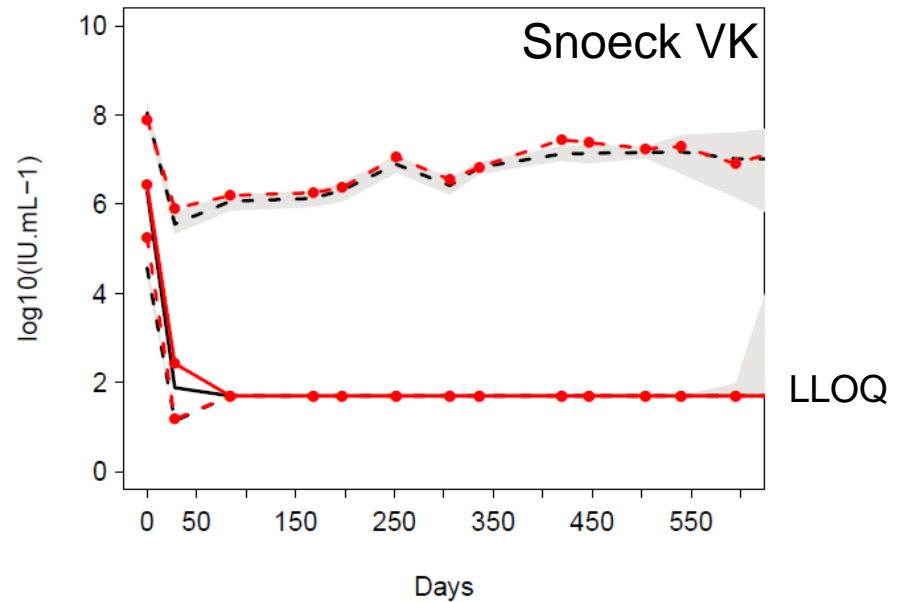
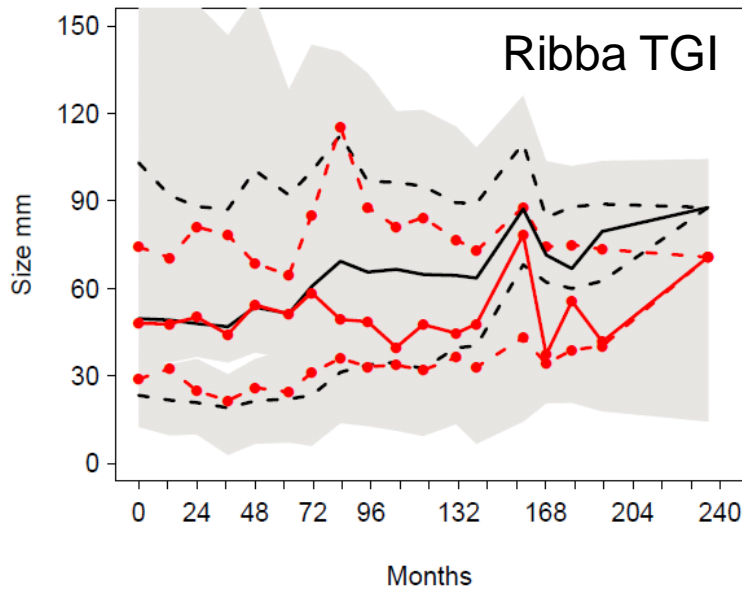
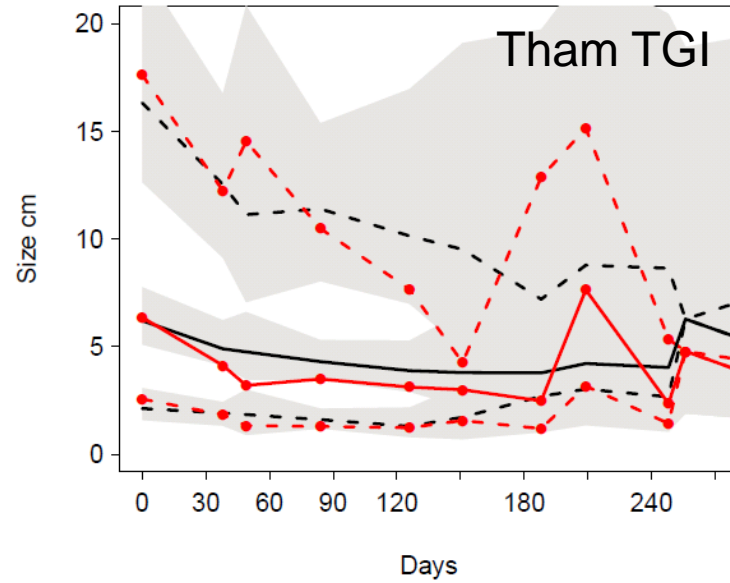
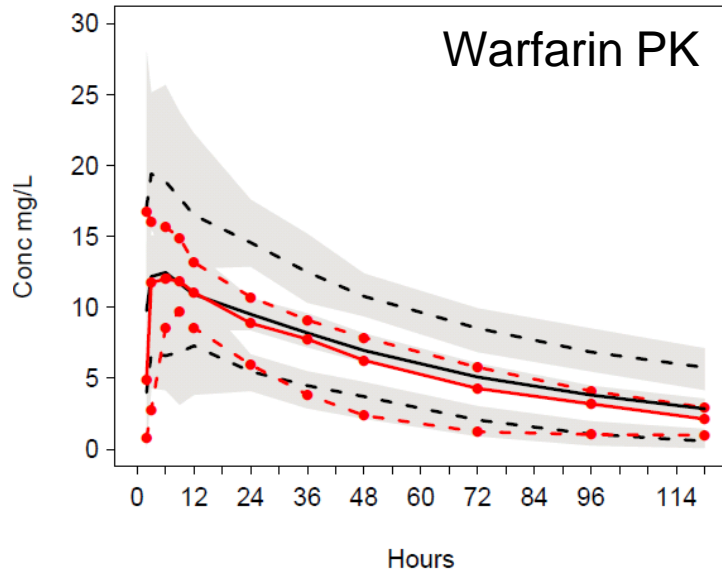


- Windows 2003 Server
 - WFN 731
- New Zealand eScience Infrastructure (NeSI) grid on the Auckland PAN cluster
 - Monolix 4.2.2
 - NONMEM 7.3
- Thanks to Lixoft and ICON (Australian Pharmacometrics Centre) for grid licences

Four Test Cases

- O'Reilly 1968 / PAGANZ workshops
 - Warfarin pharmacokinetics
- Tham 2008
 - Lung cancer tumour growth inhibition
 - NONMEM FOCE estimates
- Ribba 2012
 - Glioma tumour growth inhibition
- Snoeck 2010
 - Hepatitis C Viral kinetics

VPCs of Simulated Data



Estimation Methods and Options



- Parametric Bootstrap
 - 100 simulated data sets
- NONMEM
 - FOCEI
 - AUTO (SAEM In mu-transformed)
 - A10k1k (like AUTO but 10,000 burnin, 1,000 accumulation)
- Monolix
 - SAEM (In transformed internally)
 - p5p2 (500 burnin, 200 accumulation)
 - A10k1k (like p5p2 but 10,000 burnin, 1,000 accumulation)

What is the Truth?



- Bias: Easy
 - True parameters for fixed and random effects used for simulation
 - Compared to bootstrap average estimate

- Uncertainty: Tricky
 - 95SE: Standard error describing the 95% bootstrap confidence interval for the parameters
 - Compared to bootstrap average asymptotic standard error

Warfarin PKPD Parameter Bias

Warfarin		NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method		FOCE	SAEM	SAEM	SAEM	SAEM
Option			AUTO	A10k1k	p5p2	A10k1k
Parameter	TRUE	MDL	MDL	MDL	MDL	MDL
POP_CL	0.1	1.5%	0.5%	0.6%	0.8%	0.8%
POP_V	8	0.3%	-0.1%	-0.1%	-0.5%	-0.5%
POP_KA	2	-15%	0.4%	-0.3%	-20%	-20%
POP_TLAG	1	-6%	-1.8%	-2.2%	-14%	-14%
RUV_ADD	1	-1.2%	-1.2%	-1.2%	-1.0%	-1.0%
RUV_PROP	0.1	1.8%	1.2%	1.5%	0.4%	0.4%
PPV_CL	0.316	-2.3%	-0.4%	-0.5%	-2.6%	-2.6%
PPV_V	0.316	-1.7%	0.4%	0.3%	30%	30%
PPV_KA	0.316	-17%	-27%	-35%	-1.4%	-1.4%
PPV_TLAG	0.316	-19%	-22%	-18%	-10%	-10%
R12	0.1	43%	23%	23%	34%	34%
Average Time	sec	13.1	37.8	39.1	55.7	53.2
Max Time	sec	63.0	117.6	101.1	89.0	85.0
Success	%	100	100	100	100	100

Warfarin PKPD Uncertainty

Warfarin	NONMEM	NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method	FOCE	FOCE	SAEM	SAEM	SAEM	SAEM
Option	INTER	INTER	AUTO	A10k1k	p5p2	A10k1k
Parameter	95 SE	AsymRSE	AsymRSE	AsymRSE	AsymRSE	AsymRSE
POP_CL	6%	-6%	23%	5%	3.6%	3.6%
POP_V	6%	-10%	16%	1.4%	0.6%	0.6%
POP_KA	24%	121%	584%	149%	6%	6%
POP_TLAG	15%	69%	257%	63%	21%	21%
RUV_ADD	6%	-1%	24%	-4%	3623%	3623%
RUV_PROP	10%	46%	109%	47%	-100%	-100%
PPV_CL	15%	2.9%	49%	4.0%	-100%	-100%
PPV_V	12%	21%	43%	18%	517%	517%
PPV_KA	70%	200%	567%	236%	-80%	-80%
PPV_TLAG	48%	113%	576%	172%	18%	18%
R12	130%					
SE success	%	26	100	100	100	100

Tham TGI Parameter Bias

Tham		NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method		FOCE	SAEM	SAEM	SAEM	SAEM
Option		INTER	AUTO	A10k1k	p5p2	A10k1k
Parameter	TRUE	MDL	MDL	MDL	MDL	MDL
POP_SIZE0	6.66	-2.9%	-27%	-31%	0.5%	0.6%
POP_TOVER	18.9	15%	258%	186%	49%	49%
POP_AE50	11700	-13%	-65%	-69%	-29%	-30%
POP_TEQ	8.27	31%	-63%	120854%	-10%	-10%
PPV_SIZE0	0.563	-0.2%	-4.2%	-0.1%	0.1%	0.1%
PPV_TOVER	0.286	-59%	56%	56%	143%	143%
PPV_AE50	1.378	-9%	35%	39%	-6%	-6%
PPV_TEQ	0.189	-2.6%	5190%	2765%	-3%	-2.9%
RUV_CV	0.110	21.5%	31101%	15062%	-6%	-6%
Average time	min	0.49	10.1	10.3	2.5	2.5
Max time	min	0.80	24.6	44.7	6.8	7.1
Success	%	100	100	100	100	100

Tham TGI Uncertainty

Tham	NONMEM	NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method	FOCE	FOCE	SAEM	SAEM	SAEM	SAEM
Option	INTER		AUTO	A10k1k	p5p2	A10k1k
Parameter	95 SE	AsymRSE	AsymRSE	AsymRSE	AsymRSE	AsymRSE
POP_SIZE0	7%	8%	2495%	946%	8%	8%
POP_TOVER	41%	-1.8%	347%	325%	30%	29%
POP_AE50	40%	-20%	468%	687%	37%	37%
POP_TEQ	47%	-40%	301%	165%	-58%	-58%
PPV_SIZE0	9%	8%	2007%	908%	9%	9%
PPV_TOVER	143%	-36%	628%	215%	-52%	-52%
PPV_AE50	21%	2.8%	4015%	1662%	32%	32%
PPV_TEQ	7%	13.1%	4324%	1821%	202227%	202227%
RUV_CV	74%	-45.2%	428%	45%	-90%	-90%
SE Success	%	15	100	100	100	100

Ribba TGI Parameter Bias

Ribba		NONMEM	NONMEM	Monolix	Monolix
Method		SAEM	SAEM	SAEM	SAEM
Option		AUTO	A10k1k	p5p2	A10k1k
Parameter	TRUE	MDL	MDL	MDL	MDL
PT0	7.13	1.5%	7%	23%	22%
Q0	41.2	-15%	-16%	-5%	-5%
LAMBDAP	0.121	48%	45%	0.5%	0.6%
KPQ	0.0295	166%	164%	0.3%	0.3%
KQPP	0.0031	836%	838%	5%	5%
DELTAQP	0.009	335%	335%	-15%	-15%
GAMA	0.729	36%	32%	9%	9%
KDE	0.240	25%	23%	-11%	-11%
a	2.930	0.05%	0%	0.3%	0.3%
omega_PT0	0.940	2.0%	-0.5%	-6%	-6%
omega_Q0	0.540	32%	33%	-6%	-6%
omega_LAMBDAP	0.720	1.9%	3.3%	-1.0%	-1.1%
omega_KPQ	0.760	22%	24%	33%	33%
omega_KQPP	0.970	-5%	-5%	25%	25%
omega_DELTAQP	0.750	14%	14%	1.7%	1.6%
omega_GAMA	1.150	0.3%	-2.0%	-12%	-12%
Average time	min	13.6	13.3	2.0	2.0

Ribba TGI Uncertainty

Ribba	Monolix	NONMEM	NONMEM	Monolix	Monolix
Method	SAEM	SAEM	SAEM	SAEM	SAEM
Option	p5p2	AUTO	A10k1k	p5p2	A10k1k
Parameter	95SE SAEM	AsymRSE	AsymRSE	AsymRSE	AsymRSE
PT0	36%	481%	22%	-4%	-5%
Q0	13%	134%	-2.9%	7%	7%
LAMBDAP	28%	444%	160%	-7%	-5%
KPQ	44%	981%	188%	18%	15%
KQPP	75%	84%	52%	29%	16%
DELTAQP	36%	243%	327%	31%	30%
GAMA	38%	308%	300%	11%	8%
KDE	42%	122%	126%	0.4%	-6.6%
a	6%	204%	132%	4%	2%
omega_PT0	31%	664%	225%	24%	24%
omega_Q0	22%	115%	153%	-8%	-9%
omega_LAMBDAP	39%	230%	376%	-18%	-19%
omega_KPQ	54%	491%	669%	1.2%	-3.2%
omega_KQPP	63%	346%	223%	20%	6%
omega_DELTAQP	45%	471%	411%	23%	16%
omega_GAMA	36%	339%	517%	-7%	-8%
SE Success	%	100	100	100	100

Snoeck VK Parameter Bias

Snoeck		NONMEM	NONMEM	Monolix	Monolix
Method		SAEM	SAEM	SAEM	SAEM
Option		AUTO	A10k1k	p5p2	A10k1k
Parameter	TRUE	MDL	MDL	MDL	MDL
POP_RR0	7.15	-1.7%	-1.5%	3.6%	3.5%
POP_P	25.1	-27%	-27%	5%	5%
POP_C	4.53	-25%	-25%	4.0%	3.7%
POP_DELTA	0.192	-0.5%	-0.4%	0.6%	0.6%
BETA_DELTA	-0.1403	0.6%	0.6%	4.4%	4.5%
POP_ED50PEG	1.190	-12%	-13%	5%	5%
BETA_ED50PEG	1.245	3.6%	3.9%	-2.6%	-2%
POP_ED50RBV	14.40	-22%	-21%	5%	5%
POP_K	0.024	10%	10%	-2.8%	-3.0%
POP_R	0.006	14%	14%	-3.2%	-3.1%
RUV_SDVL	0.510	0.4%	0.4%	0.9%	0.9%
PPV_RR0	1.370	10%	10%	-0.1%	0.0%
PPV_C	1.200	-2.5%	0.0%	-0.1%	-0.1%
PPV_DELTA	0.580	0.2%	-2.6%	0.4%	0.3%
PPV_ED50PEG	2.810	5%	0.5%	-1.4%	-1.5%
Average	hour	22.0	22.2	6.5	6.5
Max	hour	45.8	38	7.9	8.1
Successes	%	100	100	97	98

Snoeck VK Uncertainty

Snoeck	NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method	SAEM	SAEM	SAEM	SAEM	SAEM
Option	AUTO	AUTO	A10k1k	p5p2	A10k1k
Parameter	95SE SAEM	AsymRSE	AsymRSE	AsymRSE	AsymRSE
POP_RR0	10%	-40%	-40%	-41%	-41%
POP_P	10%	-99%	-99%	-76%	-77%
POP_C	9%	-61%	-61%	-43%	-44%
POP_DELTA	2.9%	19%	19%	15%	15%
BETA_DELTA	26%	16%	17%	12%	11%
POP_ED50PEG	14%	10%	9%	11%	11%
BETA_ED50PEG	14%	1.5%	0.8%	8%	8%
POP_ED50RBV	23%	-100%	-100%	-100%	-100%
POP_K	9%	-100%	-100%	-100%	-100%
POP_R	17%	-100%	-100%	-100%	-100%
RUV_SDVL	0.9%	9%	9%	-100%	-100%
PPV_RR0	4.1%	17%	16%	4.1%	4.1%
PPV_C	2.6%	-5%	0.0%	-6%	0.0%
PPV_DELTA	3.3%	1.8%	-5%	-3.4%	-6%
PPV_ED50PEG	3.2%	-3%	2.2%	-5%	-3%
SE Success	%	100	100	97	98

Conclusions



- Based on parameter and standard error bias the FOCE estimation method is better in some cases (warfarin, Tham) and SAEM is a better method in others (Ribba, Snoeck)
- Both NONMEM and Monolix asymptotic standard errors are often poor descriptions of uncertainty relative to the bootstrap 95 SE

Sources

O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs. Initiation of warfarin therapy without a loading dose. *Circulation*. 1968;38:169-77.

Tham LS, Wang L, Soo RA, Lee SC, Lee HS, Yong WP, et al. A pharmacodynamic model for the time course of tumor shrinkage by gemcitabine + carboplatin in non-small cell lung cancer patients. *Clin Cancer Res*. 2008;14(13):4213-8.

Ribba B, Kaloshi G, Peyre M. Treated with Chemotherapy or Radiotherapy. A Tumor Growth Inhibition Model for Low-Grade Glioma. *Clin Cancer Res*. 2012;doi:10.1158/1078-0432.CCR-12-0084.

Snoeck E, Chanu P, Lavielle M, Jacqmin P, Jonsson EN, Jorga K, et al. A comprehensive hepatitis C viral kinetic model explaining cure. *Clin Pharmacol Ther*. 2010;87(6):706-13.

Monolix and NONMEM



The mapping of parameters between Monolix and NONMEM SAEM is as follows:

Monolix	NONMEM SAEM
Number of Chains	ISAMPLE
K0	CONSTRAINT subroutine may be user modified to provide any constraining pattern on any population parameters
K1	NBURN
K2	NITER
Auto K1	CTYPE=1,2,3
Population Parameter settings menu:	
rho	IACCEPT
m1	ISAMPLE_M1
m2	ISAMPLE_M1A
m3	ISAMPLE_M2
m4	ISAMPLE_M3
No simulated annealing	CONSTRAIN=0
Simulated Annealing	CONSTRAIN=1,2,3 User may also define algorithm
SEED	SEED

AUTO



AUTO=0 (default) (NM73)

If option AUTO=1 is selected, then several options will be set by NONMEM that will allow best settings to be determined. The user may still override those options set by AUTO, by specifying them on the same \$EST record. For example,

```
$EST METHOD=ITS AUTO=1 PRINT=10
$EST METHOD=SAEM AUTO=1 PRINT=50
$EST METHOD=IMP PRINT=1 EONLY=1 NITER=5
ISAMPLE=1000
$EST METHOD=BAYES AUTO=1 NITER=1000 FILE=auto.txt
PRINT=100
```

The settings of AUTO for each method are as follows:

```
METHOD=DIRECT INTERACTION ISAMPLE=1000 CTYPE=3
NITER=500 STDOBJ=10
  ISAMPEND=10000 NOPRIOR=1 CITER=10 CINTERVAL=0
CALPHA=0.05
EONLY=0
```

```
METHOD=BAYES INTERACTION CTYPE=3 NITER=10000
NBURN=4000
  NOPRIOR=0 CITER=10 CINTERVAL=0 CALPHA=0.05
IACCEPT=0.4 ISCALE_MIN=1.0E-06 ISCALE_MAX=1.0E+06
  PACCEPT=0.5 PSCALE_MIN=0.01 PSCALE_MAX=1000
PSAMPLE_M1=-1 PSAMPLE_M2=-1 PSAMPLE_M3=1
OSAMPLE_M1=-1
  OSAMPLE_M2=-1 OACCEPT=0.5 ISAMPLE_M1=2
ISAMPLE_M1A=0
  ISAMPLE_M2=2 ISAMPLE_M3=3
```

```
METHOD=SAEM INTERACTION CTYPE=3 NITER=1000 NBURN=4000
  ISAMPEND=10 NOPRIOR=1 CITER=10 CINTERVAL=0
CALPHA=0.05
IACCEPT=0.4 ISCALE_MIN=1.0E-06 ISCALE_MAX=1.0E+06
  ISAMPLE_M1=2 ISAMPLE_M1A=0 ISAMPLE_M2=2 ISAMPLE_M3=2
CONSTRAN=1 EONLY=0 ISAMPLE=2
```

```
METHOD=ITS INTERACTION CTYPE=3 NITER=500
  NOPRIOR=1 CITER=10 CINTERVAL=1 CALPHA=0.05
```

```
METHOD=IMP INTERACTION CTYPE=3 NITER=500 ISAMPLE=300
  ISAMPEND=10000 NOPRIOR=1 CITER=10 CINTERVAL=1
CALPHA=0.05
  IACCEPT=0.0 ISCALE_MIN=0.1 ISCALE_MAX=10 DF=0
MCETA=3
EONLY=0 MAPITER=1 MAPINTER=-1
```

```
METHOD=IMPMAP INTERACTION CTYPE=3 NITER=500
ISAMPLE=300
  ISAMPEND=10000 NOPRIOR=1 CITER=10 CINTERVAL=1
CALPHA=0.05
  IACCEPT=0.0 ISCALE_MIN=0.1 ISCALE_MAX=10 DF=0
MCETA=3
EONLY=0
```