

Evaluation of NONMEM 7.3.0 and Monolix 4.3.2 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 733 (<http://wfn.sourceforge.net>) supports parametric and non-parametric bootstrapping of NONMEM and Monolix

What is the Right Answer?

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

Four Test Cases

O'Reilly 1968 / PAGANZ workshops

Warfarin pharmacokinetics

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

Tham 2008

Lung cancer tumour growth inhibition

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 2012

Glioma tumour growth inhibition

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 2010

Hepatitis C Viral kinetics

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.

Computation Resources

Windows 2003 Server
WFN 733

New Zealand eScience Infrastructure (NeSI) grid on the Auckland PAN cluster
Monolix 4.3.2 (4 parallel threads)
NONMEM 7.3.0 (4 parallel threads)

Estimation Methods and Options

Parametric Bootstrap
100 simulated data sets

NONMEM

FOCE!
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, Auto option)
A10k1k (like p5p2 but 10,000 burnin, 1,000 accumulation, Auto option)

Initial Estimates

- Runs were started with initial estimates equal to the parameter values used for simulation (T0)
- Runs were started with initial estimates jittered x3 or x 1/3 the parameter values used for simulation (J3)

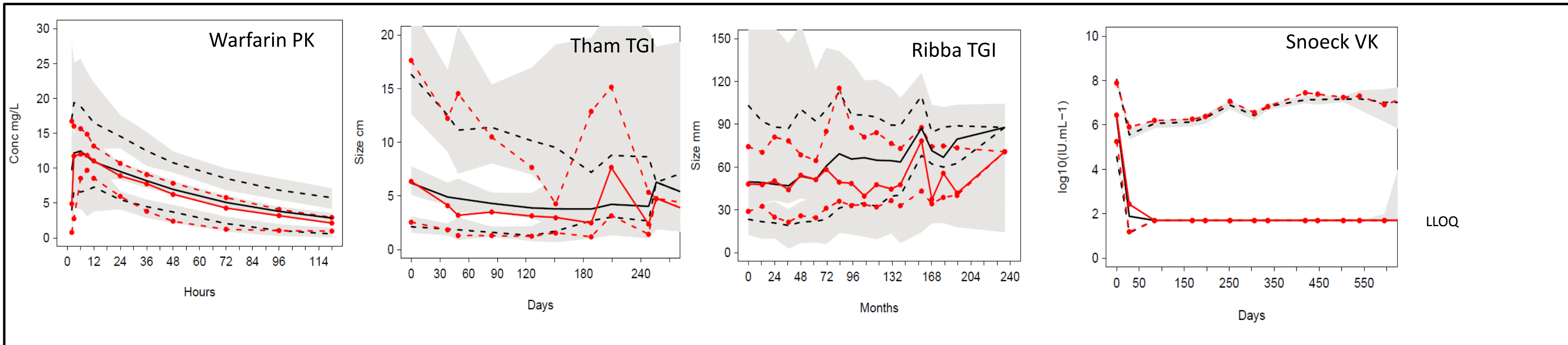
Conclusions

Based on parameter and standard error bias the FOCE estimation method is better in some cases (Tham (J3)) and SAEM is a better method in others (warfarin,Tham (T0), Ribba, Snoeck)

Both NONMEM and Monolix asymptotic standard errors are often poor descriptions of uncertainty relative to the bootstrap 95 SE

Results

VPCs of Simulated Data



Parameter Bias

Warfarin T0		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_CL	0.1	1.5%	0.54%	0.55%	0.84%	0.84%
POP_V	8	0.33%	-0.07%	-0.07%	-0.49%	-0.49%
POP_KA	2	-15%	0.4%	-0.30%	-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%	0.44%	0.44%
PPV_CL	0.316	-2.3%	-0.41%	-0.46%	-2.6%	-2.6%
PPV_V	0.316	-1.7%	0.43%	0.35%	30%	30%
PPV_KA	0.316	-17%	-27%	-35%	-1.4%	-1.4%
PPV_TLAG	0.316	-19%	-22%	-18%	-10%	-10%
Corr CL V	0.1	43%	23%	23%	34%	34%
Average Time	sec	13.1	37.8	39.1	32.8	35.5
Max Time	sec	63.0	117.6	101.1	55.0	60.0
Success	%	100	100	100	100	100

Parameter Uncertainty

Warfarin T0	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%	1.3%	1.3%
POP_KA	24%	121%	584%	149%	23%	23%
POP_TLAG	15%	69%	257%	63%	22%	22%
RUV_ADD	6%	-0.76%	24%	-4.3%	3422%	3422%
RUV_PROP	10%	46%	109%	47%	-25%	-25%
PPV_CL	15%	2.9%	49%	4.0%	-1.6%	-1.6%
PPV_V	12%	21%	43%	18%	511%	511%
PPV_KA	70%	200%	567%	236%	-80%	-80%
PPV_TLAG	48%	113%	576%	172%	59%	59%
Corr CL V	130%					
SE success	%	26	100	100	100	100

Tham T0		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	6.39	1.1%	3.7%	3.7%	3.4%	3.4%
POP_TOVER	33.9	-37%	20%	15%	76%	76%
POP_AE50	6324	60%	3.5%	3.5%	-42%	-42%
POP_TEQ	4.407	111%	23%	21%	-5%	-5%
PPV_SIZE0	0.6	-7%	-6%	-6%	-6.3%	-6.3%
PPV_TOVER	0.420	-72%	29%	17%	90%	90%
PPV_AE50	1.200	4.0%	29%	32%	32%	32%
PPV_TEQ	0.200	-64%	62%	48%	218%	218%
RUV_CV	0.199	-3.9%	-5%	-5%	-4.7%	-4.7%
Average time	min	0.51	9.8	10.6	1.7	1.7
Max time	min	1.00	22.3	38.6	2.7	2.9
Success	%	100	100	100	100	100

Tham T0	NONMEM	NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method	SAEM InMU	FOCE	SAEM	SAEM	SAEM	SAEM
Option	A10k1k	AUTO	AUTO	A10k1k	p5p2	A10k1k
Parameter	95SE SAEM	AsymRSE	AsymRSE	AsymRSE	AsymRSE	AsymRSE
POP_SIZE0	7%	-3.4%	24%	35.7%	6%	6%
POP_TOVER	58%	-5.2%	130%	71%	-13%	-13%
POP_AE50	64%	-4.7%	136%	115%	12%	12%
POP_TEQ	65%	-40%	0.26%	36%	-10%	-10%
PPV_SIZE0	10%	-8%	37%	18%	8%	8%
PPV_TOVER	104%	166%	691%	577%	-50%	-50%
PPV_AE50	43%	-48%	283%	131%	10%	10%
PPV_TEQ	145%	-6.2%	128%	77%	-41%	-41%
RUV_CV	5%	32%	196%	60%	22%	22%
SE Success	%	6	100	100	100	100

Ribba T0		NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method		FOCE	SAEM	SAEM	SAEM	SAEM
Option		STD	AUTO	A10k1k	p5p2	A10k1k
Parameter	TRUE	MDL	MDL	MDL	MDL	MDL
PTO	7.13	23%	1.5%	7%	23%	23%
Q0	41.2	1.3%	-15%	-16%	-5%	-5%
LAMBDAP	0.121	3.7%	48%	45%	-3.1%	-2.9%
KPQ	0.0295	11%	166%	164%	-6.1%	-5.9%
KQPP	0.0031	35%	836%	838%	1.5%	1.4%
DELTAQ	0.009	13.2%	335%	335%	-11%	-11%
GAMA	0.729	2.6%	36%	32%	10%	10%
KDE	0.240	75%	25%	23%	-3.1%	-3.0%
a	2.930	0.061%	0.048%	0.15%	0.52%	0.51%
omega_PTO	0.940	-20%	2.0%	-0.5%	-0.52%	-0.71%
omega_Q0	0.540	-3.9%	32%	33%	-7%	-7%
omega_LAMBDAP	0.720	-12%	1.9%	3.3%	-0.12%	-0.17%
omega_KPQ	0.760	-24%	22%	24%	28%	28%
omega_KQPP	0.970	-16%	-5%	-5%	28%	28%
omega_DELTAQ	0.750	-24%	14%	14%	-5%	-5%
omega_GAMA	1.150	-19%	0.35%	-2.0%	-11%	-11%
Average time	min	3.5	13.6	13.3	1.9	1.9
Max time	min	3.5	34.9	45.1	3.5	2.9
Success	%	100	100	100	100	100

Ribba T0	Monolix	NONMEM	NONMEM	NONMEM	Monolix	Monolix
Method	SAEM	FOCE	SAEM	SAEM	SAEM	SAEM
Option	p5p2	STD	AUTO	A10k1k	p5p2	A10k1k
Parameter	95SE SAEM	AsymRSE	AsymRSE	AsymRSE	AsymRSE	AsymRSE
PTO	38%	-21%	447%	15%	2.2%	8%
Q0	14%	-4.56%	112%	-12%	-4.1%	0.59%
LAMBDAP	28%	-13%	445%	161%	4.5%	2.7%
KPQ	42%	-13%	1032%	202%	9%	10%
KQPP	67%	-5%	103%	68%	82%	90%
DELTAQ	39%	3%	215%	292%	13%	23%
GAMA	53%	-28%	196%	190%	-10%	-13%
KDE	49.9%	-11%	86%	89%	-6.8%	-8.7%
a	5%	-2%	233%	154%	10%	10%
omega_PTO	31%	25%	665%	225%	23%	28%
omega_Q0	24%	-8%	92%	126%	-18%	-13%
omega_LAMBDAP	35%	18%	269%	432%	14%	11%
omega_KPQ	46%	58%	584%	790%	28%	25%
omega_KQPP	75%	616%	275%	172%	-0.43%	6%
omega_DELTAQ	36%	166%	609%	535%	60%	68%
omega_GAMA	42%	4%	278%	432%	-4%	-7%
SE Success	%	31	100	100	100	100

Snoeck T0		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%	4.0%	4.0%
POP_P	25.1	-27%	-27%	3.9%	4.2%
POP_C	4.53	-25%	-25%	3.2%	3.4%
POP_DELTA	0.192	-0.54%	-0.40%	0.12%	0.22%
BETA_DELTA	-0.1403	0.59%	0.61%	3.8%	3.3%
POP_ED50PEG	1.190	-12%	-13%	3.7%	4.1%
BETA_ED50PEG	1.245	3.6%	3.9%	-2.0%	-1.9%
POP_ED50RBV	14.40	-22%	-21%	5%	5%
POP_K	0.024	10%	10%	-4.0%	-3.8%
POP_R	0.006	14%	14%	-3.1%	-3.2%
RUV_SDVL	0.510	0.40%	0.36%	0.8%	0.8%
PPV_RR0	1.370	10%	10%	-0.84%	-0.69%
PPV_C	1.200	-2.5%	0.00%	-0.23%	-0.17%
PPV_DELTA	0.580	0.25%	-2.6%	-0.02%	0.23%
PPV_ED50PEG	2.810	5%	0.46%	-1.0%	-1.1%
Average	hour	22.0	22.2	6.2	6.2
Max	hour	45.8	38	7.6	7.8
Success	%	100	100	94	93

Snoeck T0	Monolix	NONMEM	NONMEM	Monolix	Monolix
Method	SAEM	SAEM	SAEM	SAEM	SAEM
Option	A10k1k	AUTO	A10k1k	p5p2	A10k1k
Parameter	95SE SAEM	AsymRSE	AsymRSE	AsymRSE	AsymRSE
POP_RR0	7%	-16%	-16%	-17%	-17%
POP_P	11%	-99%	-99%	-73%	-74%
POP_C	11%	-68%	-68%	-51%	-51%
POP_DELTA	3%	18%	19%	15%	15%
BETA_DELTA	25%	17%	18%	12%	12%
POP_ED50PEG	15%	0.69%	-0.06%	1.6%	1.6%
BETA_ED50PEG	14%	-0.24%	-0.9%	5%	6%
POP_ED50RBV	8%	-100%	-100%	-100%	-100%
POP_K	8%	-100%	-100%	-100%	-100%
POP_R	8%	-100%	-100%	-100%	-100%
RUV_SDVL	1%	-2.6%	-2.7%	-2.8%	-3.1%
PPV_RR0	6%	-14%	-14%	-23%	-23%
PPV_C	3%	-18%	0.00%	-18%	0.00%
PPV_DELTA	3%	-1.6%	-18%	-7%	-18%
PPV_ED50PEG	4%	-18%	-1.3%	-19%	-7%
SE Success	%		100	100	94

Thanks to Lixoft and ICON (Australian Pharmacometrics Centre) for grid licences.