Improvements and New Estimation Methods in NONMEM 7 for PK/PD Population Analysis

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General Improvements in NONMEM 7

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- Exact likelihood maximization methods, such as importance sampling expectation maximization (EM), and stochastic approximation EM.
- Three stage hierarchical Markov Chain Monte Carlo (MCMC) Bayesian methods
- Improved incidence of completion when using the multiple problem feature.
- Improved efficiency and incidence of success in problems using the classical NONMEM method:
  - Recovery from positive definiteness errors
  - User controlled gradient precision

Improved Input/Output Processing in NM 7

- Additional output files, with number of significant digits selectable by the user, and which can be easily read by post-processing programs.
- Number of data items per data record increased to 50.
- Label names may be as large as 20 characters.
- Initial parameter entries in the control stream file may be of any numerical format.
- Additional post-processing diagnostics:
  - Conditional weighted residual (CWRES)
  - Normalized prediction distribution error (NPDE)
  - Exact (Monte Carlo assessed) weighted residual (EWRES)

Example Control Stream File


```
$INPUT      ID DOSE TIME LOGCONC=DV WT

$THETA  (.134555567887666,3,5) (8.0E-03,.08,.5)
(.004,.04,.9)
$OMEGA BLOCK(3)  6 .005 2.0E-04 .3 .006 .4
$EST     METHOD=ITS NITER=20 PRINT=5
         FORMAT=s1PG12.5 FILE=its.ext
$EST     METHOD=BAYES NBURN=4000 NITER=10000 PRINT=100
         FORMAT=,1PE13.6 FILE=bayes.ext
$COV
$TABLE           ID DOSE WT TIME LOGCONC EWRES CWRES NPDE
                 FILE=control4.tab FORMAT=,1PE15.8
```

Example of Table File

- FORMAT=,1PE15.8

```
TABLE NO.  2
 ID              ,CL              ,V1              ,Q               ,V2
  1.00000000E+00, 5.69092623E+00, 5.12720827E+00, 2.20089392E+00, 1.26218095E+01
  2.00000000E+00, 3.21985213E+00, 8.60898334E+00, 2.07804975E+00, 1.84545505E+01
  3.00000000E+00, 5.88308308E+00, 4.48650336E+00, 1.67072273E+00, 8.54222996E+00
  4.00000000E+00, 4.45660498E+00, 6.29850980E+00, 1.62718426E+00, 7.34878729E+00
  5.00000000E+00, 8.49889451E+00, 6.36323112E+00, 1.49701435E+00, 1.19809212E+01
  6.00000000E+00, 6.54795619E+00, 4.49423904E+00, 2.02487448E+00, 1.15981230E+01
  7.00000000E+00, 5.31196175E+00, 3.74116253E+00, 1.99124504E+00, 9.91325858E+00
```

Shrinkage Reported in Results Output File


```
#TERM:
OPTIMIZATION COMPLETED


ETABAR:    0.15E-05 -0.10E-06 -0.52E-06  0.54E-06
SE:        0.39E-01  0.29E-01  0.36E-01  0.34E-01

P VAL.:    0.10E+01  0.10E+01  0.10E+01  0.10E+01

ETAshrink:    0.33E+01  0.19E+02  0.22E+02  0.14E+02
EPSshrink:    0.32E+02

#TERE:
```

Improvements in Gradient Processing for FOCE

- In Old NONMEM:
  - SIGDIGITS (NSIG) defined convergence criterion
  - SIGDIGITS defined step size of numerical gradients for optimizing objective function
  - When gradient step size=NSIG=3
  - precision of gradient could be 2*NSIG=6
  - True only if OBJ evaluated to 3*NSIG=9
  - Internal precision of OBJ evaluated was set at 10
- This setup was okay for most analytical problems
- For numerical integration problems:
  - Internal precision based on user specified TOL
  - Often TOL=6 or less, not 10
  - Maximum gradient precision is 4.
  - NSIG should not be >2.
- Result: NONMEM sometimes runs excessively, thinking precision achievable greater than actual.

Improvements in Gradient Processing for FOCE

- In New NONMEM:
  - User tells NONMEM the precision it should evaluate the OBJ using SIGL:
- Rule of Thumb to set SIGL and NSIG (but trial and error is always good to do)
- For Analytical Problems
  - SIGL<=14 (about the limit of double precision)
  - NSIG<=SIGL/3
- For Numerical Integration problems
  - SIGL<=TOL
  - NSIG<=SIGL/3
  - So, if TOL=6, then SIGL should be 6, and NSIG should be 2

Improved Performance of Classical NONMEM

- Problem with eight parameters, three differential equations, 50 subjects

Computation Times in Hours Using FOCEI Method (not including $COV step)

Advan method	NM6: NSIG=3 TOL=6	NM7 NSIG=2 TOL=6 SIGL=6	NM7 NSIG=1 TOL=4 SIGL=3
9	>30	22	10
6	>24	17	3
13 (new)	>20	8.5	2

- By comparison, importance sampling took 30 minutes, including $COV R matrix evaluation

Example 1: Two Compartment Model with Very Sparse Sampling Analyzed by SAEM and Importance Sampling

Two Compartment, Sparse Data

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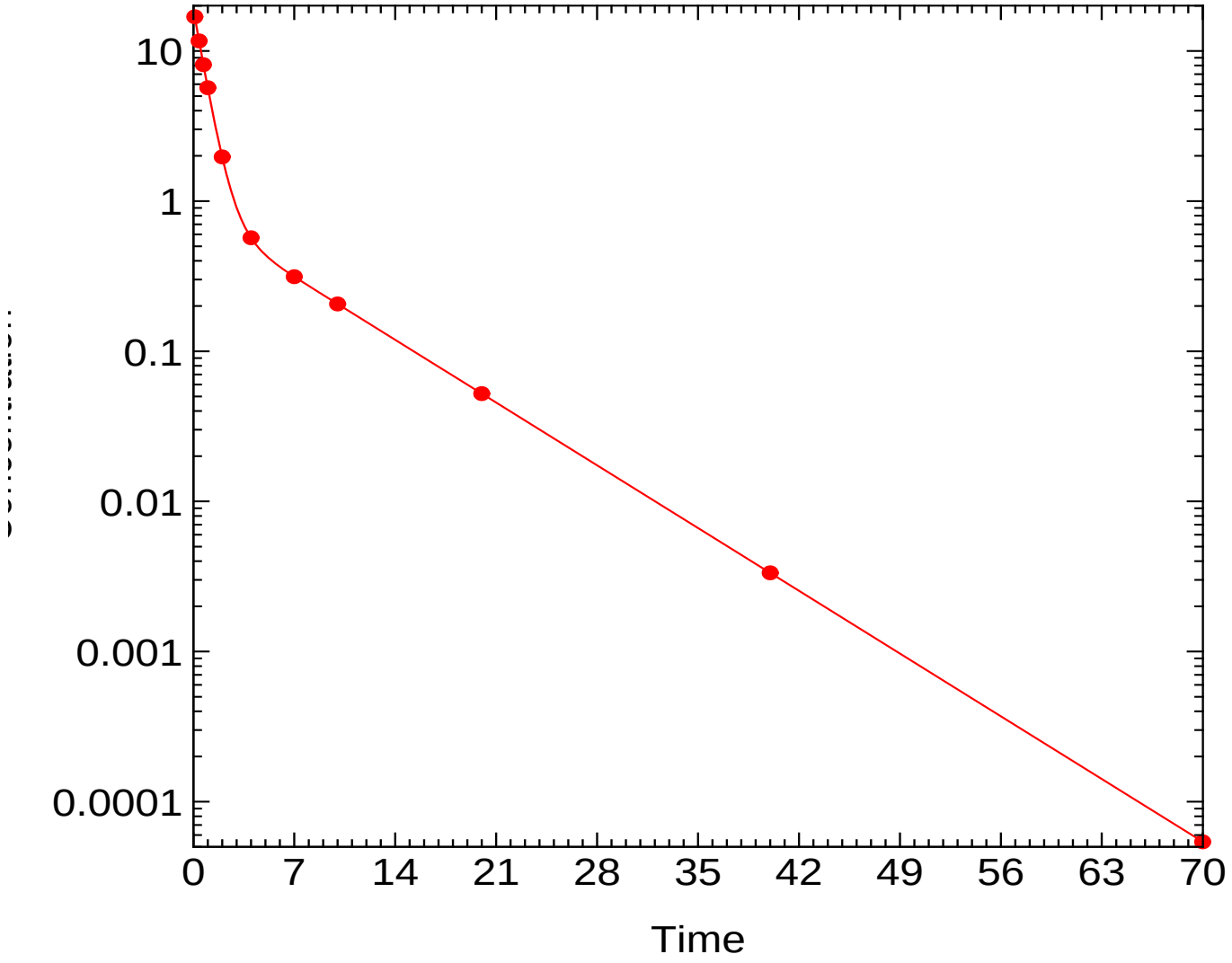
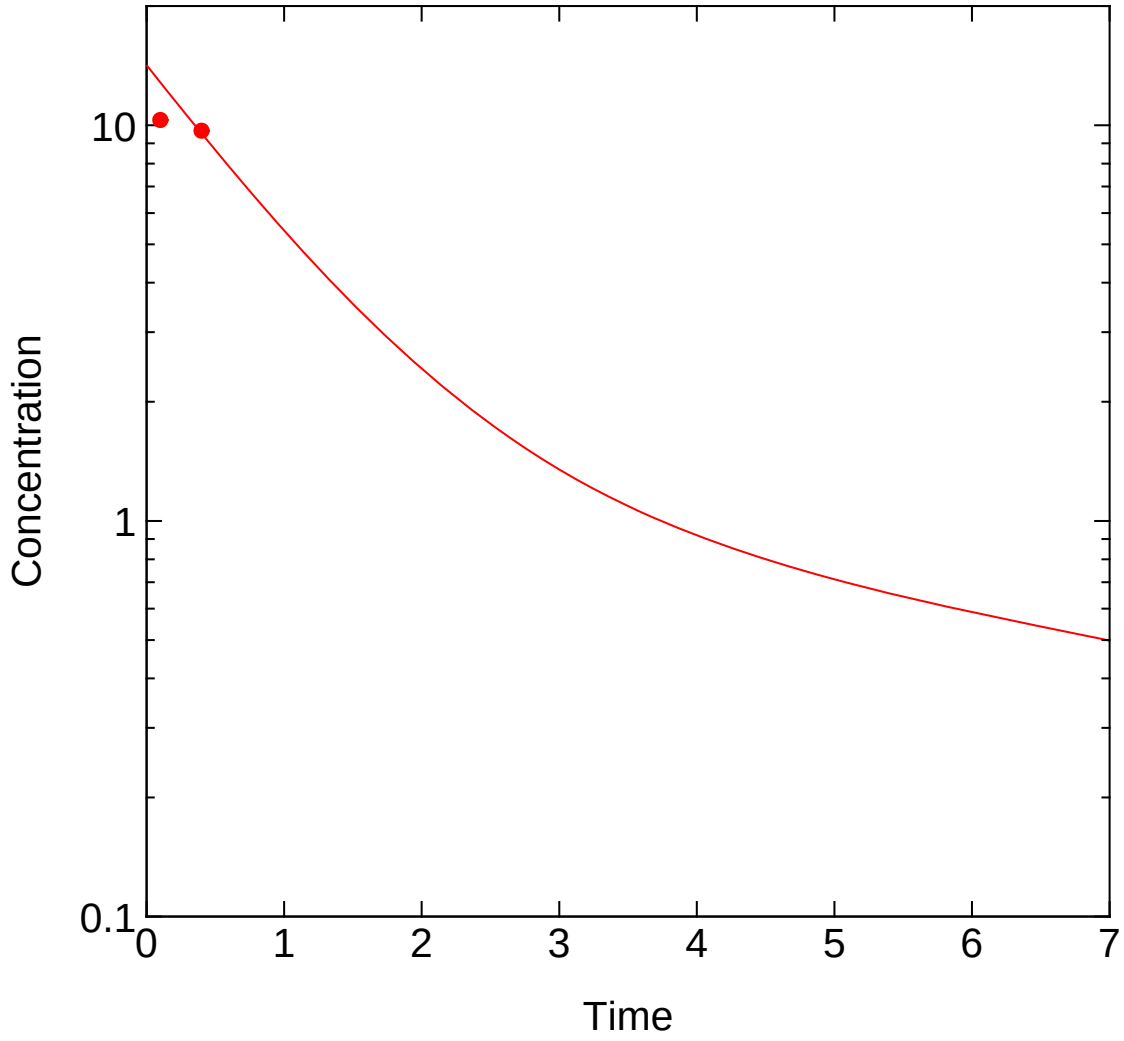
- Two-compartment PK model (parameters Log(CL), LOG(V), LOG(Q),LOG(V2))
- Single IV Bolus Dose (100 units)
- Parameters log-normally multi-variate distributed among subjects:
  - 38% CV for each of the four parameters (Omega=0.15)
- Residual Error: Proportionate error of 25% CV (S=0.0625)
- 100 data sets
- 1000 subjects per data set
- For each subject, two sampling times selected from discrete times:
  - 0.1, 0.2, 0.4, 0.7, 1, 2, 4, 7, 10, 20, 40, and 70 time units.
- All pairs of times equally represented among the subjects:
  - As there are (12x11)/2=66 combinations, there were 1000/66=15 subjects for each sample time combination.

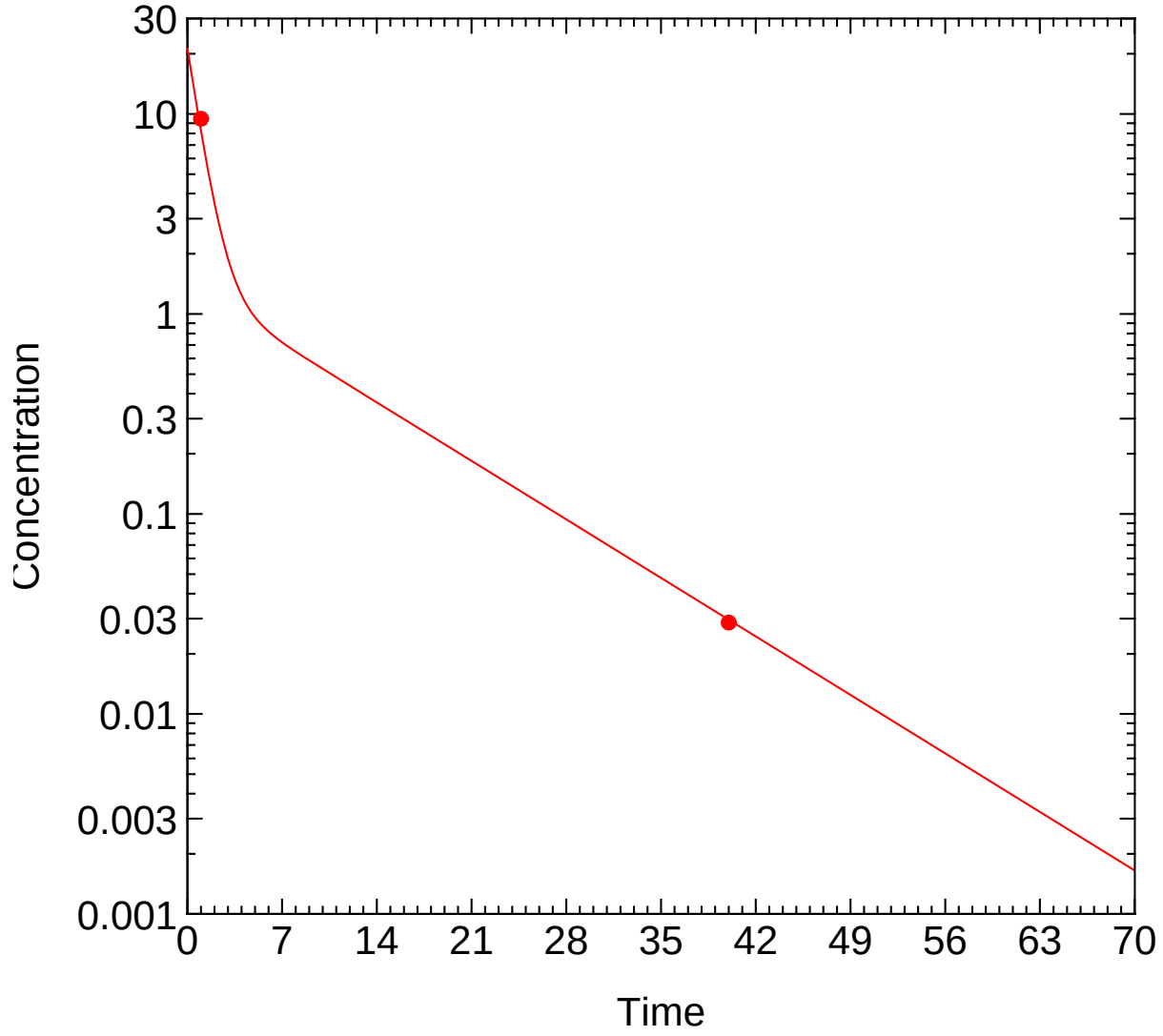
Layout of All Time Points



Layout of Time Points Subject With Close Data Points



Layout of Time Points
Subject with Far Apart Data Points



SAEM Setup

- Burn-in iterations: 2000
- Accumulation iterations: 2000
- For each Subject, Retained samples: 2
- Mode 1 sampling: 2
- Mode 2 sampling: 3
- Mode 3 sampling: 3
- MCMC Acceptance rate: 0.4

Importance Sampling Setup

- Number of random samples per subject:
  - 300 for optimization
  - 3000 for last 20 iterations
- Proposal density was t-distribution with 4 degrees of freedom
- Sampling Efficiency (equivalent to acceptance rate)=1

Two Compartment, Sparse Data, Results SAEM, N=100

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Statistic	CL	V1	Q	V2	S	VarCL	VarV1	VarQ	VarV2
Mean Reference	1.606	1.610	0.694	2.306	0.063	0.151	0.150	0.149	0.149
Mean Estimate	1.605	1.605	0.705	2.311	0.064	0.150	0.149	0.128	0.144
Var. of Estimate (%)	0.987	1.666	8.528	1.771	10.712	8.499	16.500	54.384	29.721
Avg. Standard Error (%)	0.990	1.578	6.453	1.528	10.770	7.927	15.700	36.477	27.268
Bias (%)	-0.063	-0.311	1.503	0.221	2.417	-0.206	-0.618	-13.700	-3.489
STD of %Bias	0.988	1.690	8.787	1.789	11.236	8.484	16.412	48.912	28.898
P-value	0.528	0.069	0.090	0.220	0.034	0.809	0.707	0.006	0.230

Two Compartment, Sparse Data, Results IMP, N=100

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Statistic	CL	V1	Q	V2	S	VarCL	VarV1	VarQ	VarV2
Mean Reference	1.606	1.610	0.694	2.306	0.063	0.151	0.150	0.149	0.149
Mean Estimate	1.606	1.604	0.698	2.307	0.062	0.151	0.151	0.144	0.162
Var. of Estimate (%)	0.964	1.680	7.442	1.511	9.581	8.207	15.020	33.943	20.785
Avg. Standard Error (%)	1.000	1.608	6.924	1.622	10.905	7.658	15.870	44.927	23.376
Bias (%)	-0.011	-0.343	0.463	0.071	-0.852	0.166	0.319	-3.487	8.335
STD of %Bias	0.964	1.709	7.491	1.514	9.538	8.222	15.073	32.946	24.025
P-value	0.912	0.048	0.538	0.642	0.374	0.840	0.833	0.292	0.001

Conclusions of Example 1

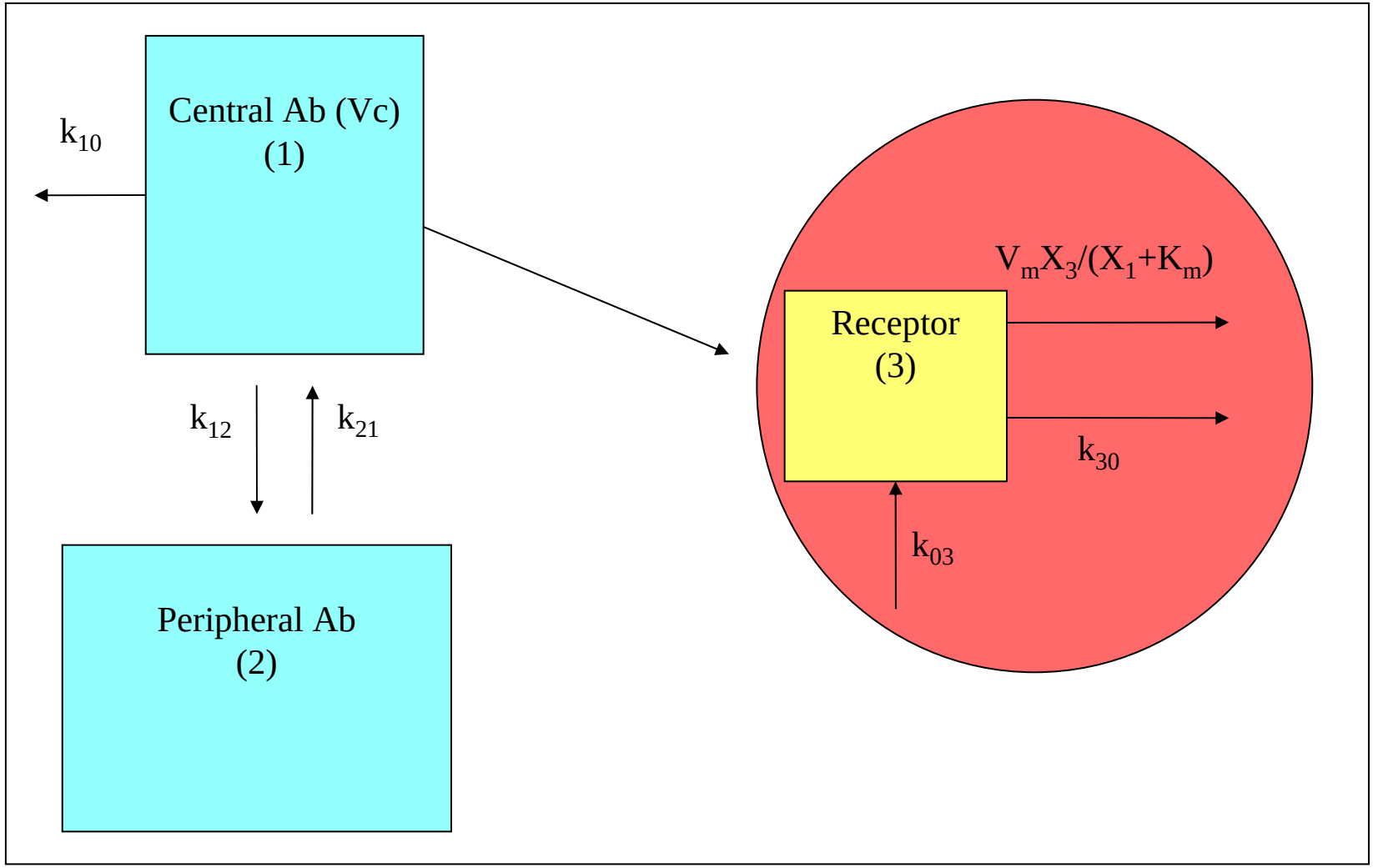
- Both SAEM and Importance Sampling provided results with low bias among the primary parameters (<2.5%)
- Both methods yielded biases in Omegas of less than 15%
- The bias was less than 25% of the typical standard error evaluated by a second order information matrix
- For SAEM, there was statistically significant bias (p-value<0.05) in residual variance (S), and VAR(Q)
- For IMP, there was statistically significant bias in V1 and Var(V2)
- The reported standard errors were on average very similar to the standard deviation of estimated values among the 100 data sets

Example 2: Complex PK/PD Model Evaluated by MCMC Bayesian Analysis

Complex PK/PD Model, Bayesian Analysis

- PK: Two compartment, with first-order and receptor-mediated clearance
- PD: indirect response
- 46 population parameters, variances/covariances, and residual error coefficients
- Three mass transfer differential equations
- 50 Subjects
- 17 PK, 18 PD samples per subject (rich data sampling)
- Gibbs sampling performed in NONMEM 7 and WinBUGS

Complex PK/PD Model, Bayesian Analysis



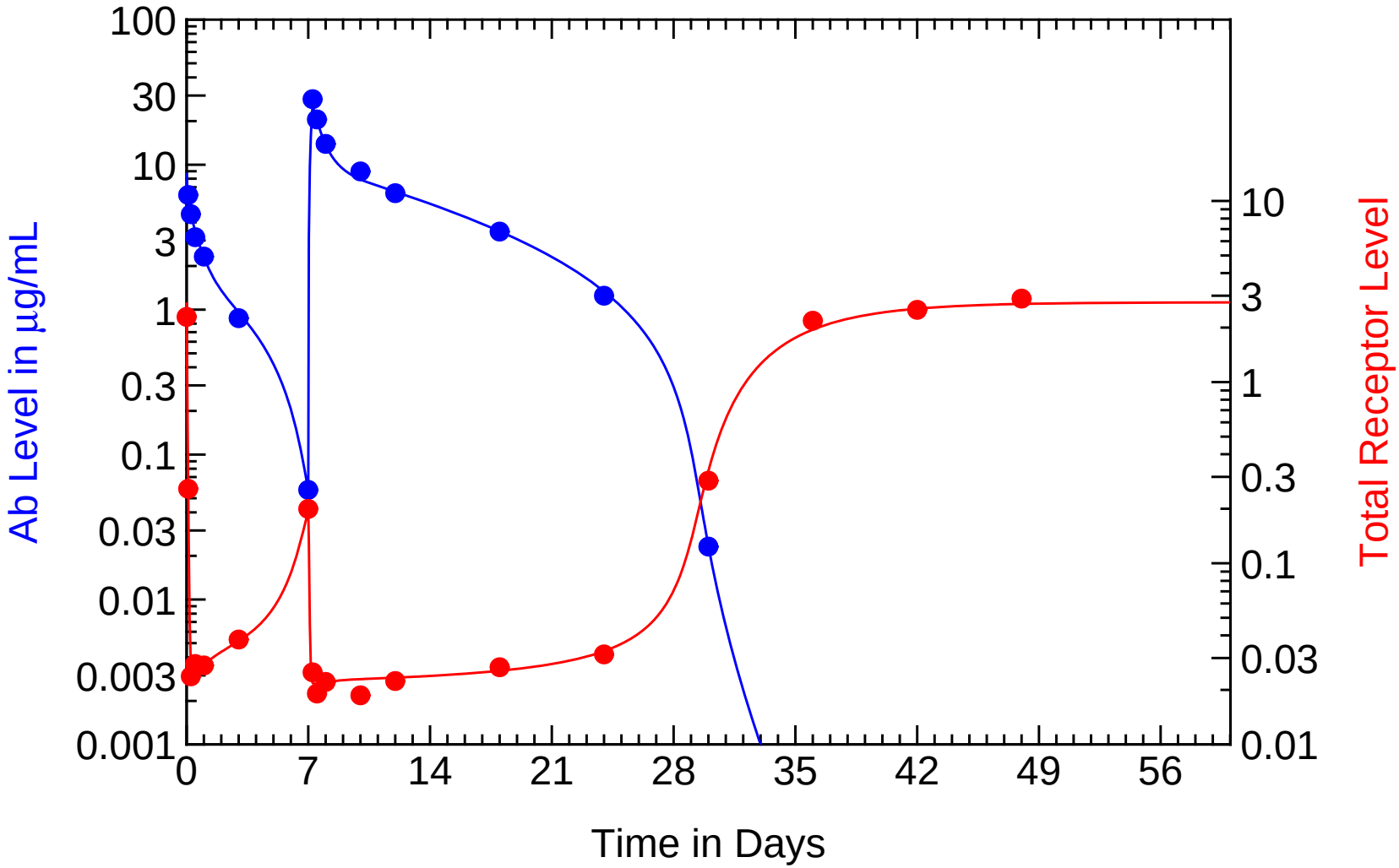
Complex PK/PD Model, Bayesian Analysis

$$\frac{dX_1}{dt} = -(K_{10} + K_{12})X_1 + K_{21}X_2 - \frac{V_m X_1 X_3}{X_1 + K_{mc} V_c} + R_1$$

$$\frac{dX_2}{dt} = K_{12}X_1 - K_{21}X_2$$

$$\frac{dX_3}{dt} = -\frac{V_m X_1 X_3}{X_1 + K_{mc} V_c} - K_{30}X_3 + K_{03}$$

Typical PK/PD Profile of Active Ab in Humans



Analysis Setup

- NONMEM and WinBUGS used 4000 iterations as burn-in period followed by 30,000 sampling iterations.
- NONMEM typically required 1.1-1.8 times longer than WinBUGS, depending on the TOL (4-8) and ADVAN (9 or 13) settings.

NONMEM Versus WinBUGS Results

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	Vc	K10	K12	K21	Vm	Kmc	K03	K30	SD1	SD2
Mean WinBUGS	49.939	0.109	1.739	0.835	9.688	1.275	40.926	0.495	0.097	0.150
Mean NONMEM	49.911	0.109	1.731	0.832	9.661	1.269	40.954	0.496	0.096	0.150
SE WinBUGS	3.822	0.008	0.104	0.063	0.645	0.099	2.934	0.035	0.003	0.004
SE NONMEM	3.838	0.008	0.107	0.062	0.640	0.096	2.943	0.035	0.003	0.004
Percent Mean Difference	-0.06%	-0.16%	-0.43%	-0.36%	-0.28%	-0.52%	0.07%	0.23%	-0.05%	0.10%

	Ω_{VC}	Ω_{K10}	Ω_{K12}	Ω_{K21}	Ω_{Vm}	Ω_{Kmc}	Ω_{K03}	Ω_{K30}
Mean WinBUGS	0.286	0.222	0.145	0.271	0.212	0.245	0.252	0.243
Mean NONMEM	0.288	0.220	0.152	0.265	0.211	0.241	0.253	0.242
SE WinBUGS	0.060	0.060	0.036	0.061	0.046	0.061	0.053	0.053
SE NONMEM	0.061	0.056	0.038	0.060	0.046	0.058	0.054	0.053
Percent Mean Difference	0.53%	-1.29%	4.74%	-2.13%	-0.77%	-1.58%	0.52%	-0.41%

K10 Bayesian Sampling History and Cumulative Distribution

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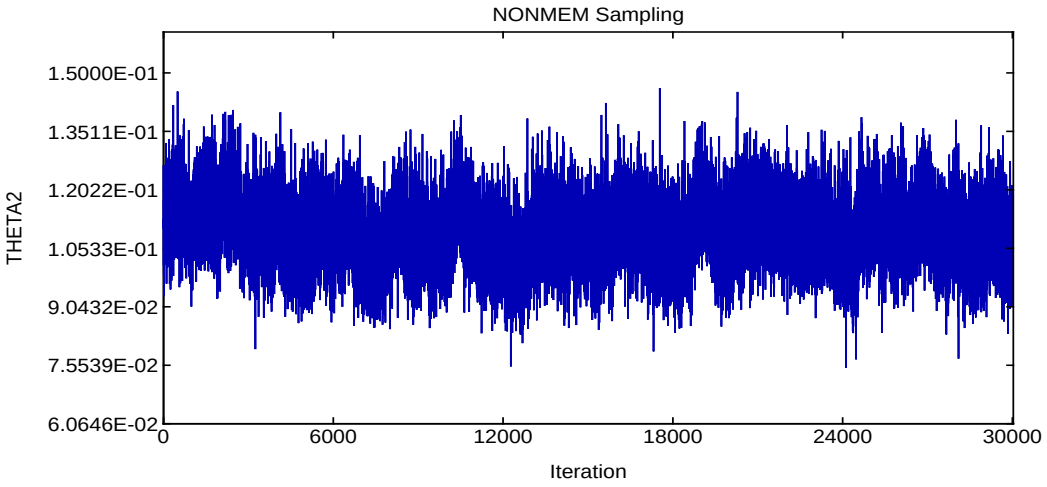

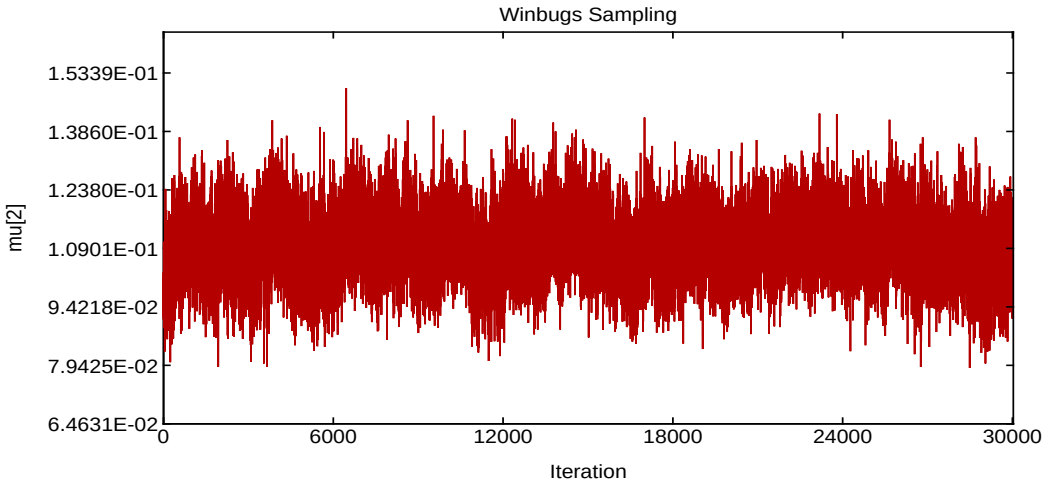

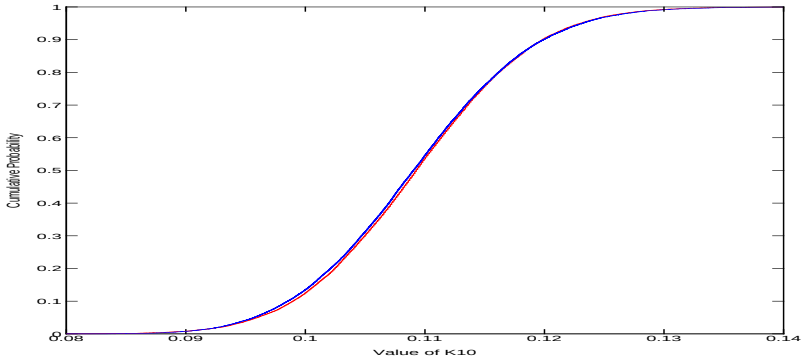

Results of Example 2

- For all parameters, extensive random mixing occurred in NONMEM and WinBUGS sampling history (See figures to the right on select parameters).
- The mean difference between sorted samples generated from NONMEM and WinBUGS were less than 1% of the sample means for THETAs and SIGMAs, and <5% of the sample means for OMEGAs.
- Analysis by FOCEI method resulted in similar values as those obtained from Bayesian Analysis, and required 7-9 hours to perform the estimation method, without the covariance step, compared to 4-5 hours for Bayesian analysis

Example 3: Variable Zero Order Input: Monte Carlo EM, SAEM, and FOCEI Methods

Modeled Zero Order Input

- Two compartment model (central and peripheral)
- First-order input from a depot compartment
- Zero-order input into the central compartment.
- Represents a study comparing a zero-order release product and a separate first-order release product.

Simulation Setup

- Clearance: CL, 5 L/hr
- Central Volume: V2, 20 L
- Peripheral Volume: V3, 10 L
- Intercompartmental Clearance: Q, 2 L
- First-order rate constant, depot to central: KA, 1.2 hr-1
- Relative bioavailability of first-order product: F1, 0.5
- Duration of input of zero-order product: D2, 0.55 hr

Simulation Setup

- Interindividual variability:
- CV ~ 30% for CL, V2, V3, Q, KA
- CV ~ 10% for F1
- CV ~ 15% for D2
- Residual error:
- CV ~ 10%

Simulation Setup

- Individuals: 102: Total observations: 2142
- Dosing: Separate dosing of each product with washout between.
- Each dosing period included multiple single daily doses followed by steady-state dosing.
- Observation (sampling times varied among individuals) for each dosing period:
  - ~5 after first dose
  - ~3 during multiple single doses
  - ~5 after final steady-state dose

Analysis Setup

- Simulation/Estimation performed using Superproblem feature.
- 100 replications/method
- No premature terminations

Successful Replications (%)

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Method	Estimation Step	Covariance Step
FOCE-I	71	0
FOCE-I var(D2)=0	99	94
IMP	--*	100
SAEM	--*	99

* Estimation step not assessed for “success” in the same manner as FOCEI methods.

Analysis Results

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	CL	V2	V3	Q	KA	F1	D2	o(CL)	o(V2)	o(V3)	o(Q)	o(KA)	o(F1)	o(D2)	s(1)
Nominal	1.61	3.00	2.30	0.69	0.18	-0.69	-0.60	0.090	0.090	0.090	0.090	0.090	0.010	0.023	0.010
SAEM															
Mean	1.60	2.99	2.31	0.67	0.18	-0.69	-0.60	0.090	0.092	0.090	0.092	0.088	0.010	0.023	0.010
SD	0.03	0.03	0.03	0.04	0.03	0.01	0.02	0.011	0.013	0.016	0.024	0.015	0.002	0.006	0.0004
IMP															
Mean	1.61	2.99	2.31	0.68	0.18	-0.69	-0.60	0.090	0.091	0.090	0.091	0.088	0.010	0.023	0.010
SD	0.03	0.03	0.04	0.05	0.03	0.01	0.02	0.011	0.013	0.016	0.024	0.015	0.002	0.006	0.0004
FOCE-I															
Mean	1.60	3.03	2.27	0.62	0.20	-0.69	-1.02	0.097	0.093	0.099	0.090	0.117	0.014	0.341	0.011
SD	1.0	0.05	0.05	0.08	0.11	0.05	0.34	0.021	0.016	0.022	0.080	0.111	0.016	0.247	0.001

Conclusions

- IMP and SAEM provide standard errors more reliably than FOCEI
- The ln(KA), ln(D2), var(ln(KA)), var(ln(F1)) and especially var(ln(D2) were more accurately estimated by IMP and SAEM methods.
- Variation across replicates were generally lower for IMP and SAEM versus FOCE-I

NONMEM 7 and PDx-POP 4 Development Team

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- Robert Bauer
- William Bachman
- Manjunatha Shivaiah (and Nous Infosystems team)