Comparison of MCMC simulation results using NONMEM 7 or WinBUGS with BUGSModelLibrary

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Background

- There is increasing interest in and use of Bayesian methods for PKPD modeling.
- NONMEM 7® [1] now includes the BAYES method that implements Markov chain Monte Carlo (MCMC) simulation for Bayesian modeling.
- WinBUGS [2] is a widely used MCMC simulation program for Bayesian modeling.
- BUGSModelLibrary [3, 4] is a WinBUGS add-on that provides PKPD models and model building tools. The models and data format are based on NONMEM®/NMTRAN/PREDPP conventions.

Objective

To compare the relative performance of the NONMEM 7 BAYES MCMC method with WinBUGS plus the BUGSModelLibrary by applying them to simulated data for a range of PK and PKPD models.

Methods

For each of the following test cases, 100 data sets were simulated using NONMEM 6:

label	model	dosing regimen	n^a	$n_{\text{obs}}{}^b$
ad1tr2	1 compartment IV	Bolus at time 0, followed by short infusion 24 hours later	100	10–11
ad1tr2mixture	1 compartment IV model, mixture model with two sub-populations	Bolus at time 0	300	8
ad1tr2occ	1 compartment IV model, inter-occasion variability over 3 occasions	3 sequential bolus events, marking the three occasions	250	5
ad2tr2	1 compartment with 1st order absorption	Oral bolus at time 0, followed by short IV infusion 24 hours later	200	3
ad3tr4	2 compartment IV	Bolus at time 0	100	12
ad3tr4covariate	2 compartment IV, CL & V1 are functions of age & gender	Bolus at time 0	400	5
ad3tr4sparse	2 compartment IV	Bolus at time 0	1000	2
ad4tr4	2 compartment with 1st order absorption	Oral bolus at time 0	250	3
ad11tr4	3 compartment IV	Bolus at time 0	200	10
ad12tr4	3 compartment with 1st order absorption	Bolus at time 0	400	14
comp2l	2 compartment IV PK + effect compartment & sigmoid Emax PD	Bolus at time 0	500	3–4
fflag	1 compartment with 1st order absorption PK + binary PD	Bolus at time 0	72	16

[a] n = number of individuals
[b] n_{obs} = number of observations per individual

- Weakly informative prior distributions were used for all parameters. The same priors were used for both NONMEM 7 and WinBUGS except for the mixture model probabilities in ad1tr2 (logit$(p) \sim N(0, 1.6)$ vs $p \sim$ Dirichlet$(1, 1)$) and the inter-occasion variance in ad1tr2occ ($1/\omega^2_{CLIOV} \sim$ Wishart$(0.017, 1)$ vs gamma$(0.001, 0.001)$).
- Each set was analyzed with NONMEM 7 and WinBUGS using 3 chains of 10,000 MCMC iterations each. The first 5,000 iterations from each chain were discarded. Every 4th sample was retained for analysis.
- Results were compared w.r.t. summary statistics of the MCMC samples, computation time and "effective N", i.e., an estimate of the equivalent number of independent samples from the posterior distribution[5, 6].

Results

- Summary statistics of NONMEM 7 and WinBUGS generated MCMC samples were generally comparable (Figure 1).
- For most examples effective N for the residual standard deviation (sigma) was greater for NONMEM 7 (Figure 2).
- NONMEM 7 also resulted in greater effective N for several other parameters in most of the examples. This is particularly notable in the ad2tr2, ad3tr4covariate, ad3tr4sparse, ad4tr4, fflag, and ad11tr4 examples (Figure 2).
- The only case where WinBUGS resulted in a substantially greater effective N was for the inter-occasion variance (omegaCLIOV) in the ad1tr2occ example (Figure 2).
- NONMEM 7 required more computation time than WinBUGS for ad1tr2, ad1tr2mixture, ad3tr4, ad3tr4covariate, and fflag, the most extreme case being ad1tr2mixture where NONMEM 7 required 6 times longer than WinBUGS. On the other hand WInBUGS required more time than NONMEM 7 for ad2tr2, ad3tr4sparse, ad11tr4, and ad12tr4 (Figures 3–4).

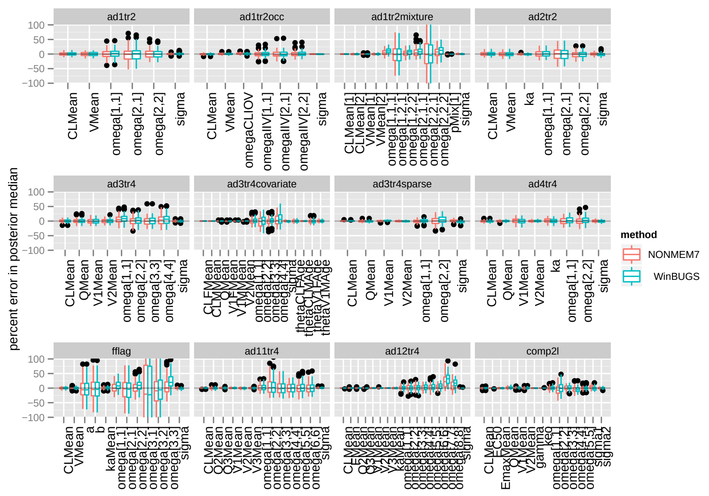

Figure 1: Distributions of percent error in the posterior medians of the MCMC samples for model parameters relative to their "true" values.

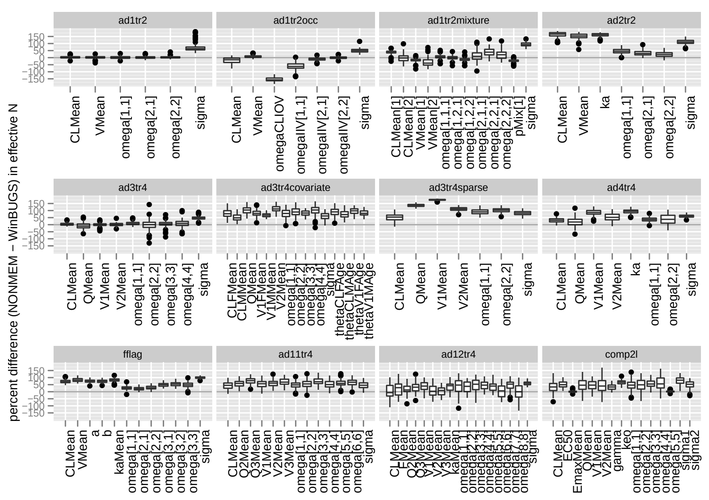

Figure 2: Distributions of percent difference between NONMEM 7 and WinBUGS in the "effective N", i.e., the equivalent number of independent samples.

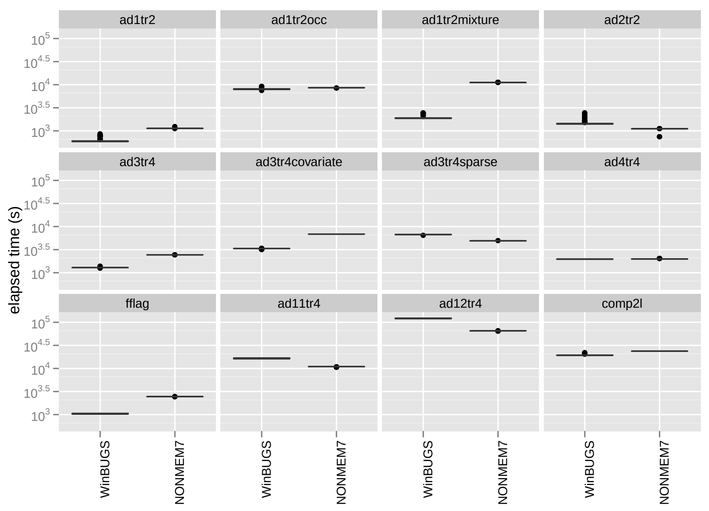

Figure 3: Distributions of computation time required for 3 MCMC chains of 10,000 iterations each.

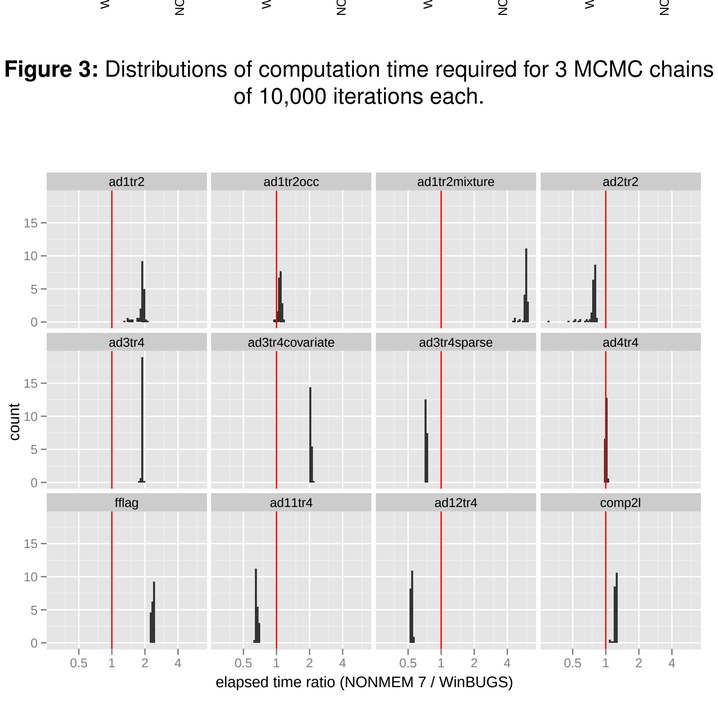

Figure 4: Distributions of the NONMEM/WinBUGS ratio of computation times required for 3 MCMC chains of 10,000 iterations each.

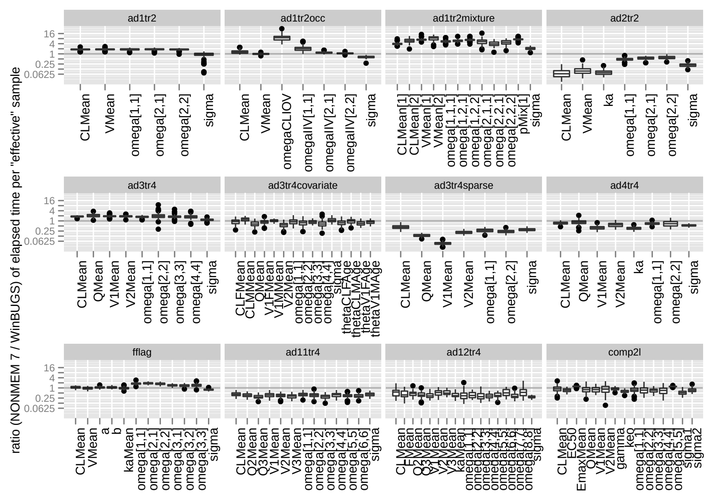

Figure 5: Distributions of the NONMEM/WinBUGS ratio of computation time per "effective" sample, i.e., $\left(\frac{\text{elapsed time}}{\text{effective N}}\right)_{\text{NONMEM}} \Big/ \left(\frac{\text{elapsed time}}{\text{effective N}}\right)_{\text{WinBUGS}}$

Conclusions

For the classes of models studied in this project:

- MCMC simulations using NONMEM 7 and WinBUGS produced results with comparable accuracy.
- NONMEM 7 produced less auto-correlated residual standard deviation samples in all cases studied.
- NONMEM 7 also produced less auto-correlated samples for several other parameters.
- WinBUGS required much less computation time to produce comparable MCMC results for a mixture model (ad1tr2mixture), and about half the computation time for the ad1tr2, ad3tr4, ad3tr4covariate, and fflag examples.
- WinBUGS required more time to produce less precise results for the ad2tr2, at4tr4, ad11tr4, and ad12tr4 examples.
- For several of the scenarios NONMEM 7 outperformed WinBUGS w.r.t. computation time adjusted for autocorrelation (Figure 5).

Recommendations

- NONMEM 7 is a recommended platform for Bayesian modeling when suitable models can be implemented within the limits imposed by NONMEM, e.g., 2 levels of random variation (3 including priors), normally-distributed IIV and priors for fixed effects, and inverse Wishart prior for the IIV variance matrix.
- An advantage of NONMEM 7 is that it provides both fully Bayesian MCMC and estimation of posterior modes within the same platform. The latter is a useful tool for accelerating Bayesian model development.
- WinBUGS is a recommended platform when greater flexibility is required w.r.t. stochastic aspects of models, e.g., when other distributions or more levels of variability are desired.
- Based on the limited testing presented here, WinBUGS appears to perform better with mixture models and models with inter-occasion variability and is the preferred platform for those cases.

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