Evaluation of software tools for Bayesian estimation on population models with count and continuous data

E. Borella[1], L. Carrara[1], S.M. Lavezzi[1], E. Mezzalana[1], L. Pasotti[1], G. De Nicolao[1], P. Magni[1]

[1]Department of Electrical, Computer and Biomedical Engineering, University of Pavia, via Ferrata 5, Pavia, I-27100, Italy

Primary contact: paolo.magni@unipv.it

BACKGROUND. In recent years, Bayesian modelling techniques have received increasing attention. Different tools have been developed to perform Bayesian estimation using Markov Chain Monte Carlo (MCMC) methods. The aim of this work is to compare five widely used tools in order to evaluate their performances and limitations on both algebraic and ordinary differential equation (ODE) population models.

METHODS.

TOOLS

WinBUGS 1.4.3 (with BlackBox Component Builder 1.5 and WBDiff interface).
RUNS ON: Windows

NONMEM 7.3.0.
RUNS ON: Windows, Linux, Mac OSX

Stan 2.5.0 with Rstan 2.5.0 interface.
RUNS ON: Windows, Linux, Mac OSX,

JAGS 3.4.0.
RUNS ON: Windows, Linux, Mac OSX,

OpenBUGS 3.2.3.
RUNS ON: Windows, Unix/Linux, Mac (using Wine)

Effective Sample Size (ESS) per execution time (in seconds) was used as a performance index to compare the different tools. It gives an estimate of the equivalent number of independent samples of the chain per time.

$$\frac{ESS}{Time} = \frac{n}{1+2\sum_{k=1}^{\infty}\rho_k}\cdot\frac{1}{Time}$$

n = original sample size
ρ_k= autocorrelation function at lag k

Estimation was performed on Windows 7 using an ASUS laptop with Intel Core i7 (2.2GHz) 6GB RAM.
R *coda* package was used to analyze Markov Chains

MODELS

ALGEBRAIC MODEL

A Poisson count model concerning a randomized clinical trial of an anticonvulsant for epilepsy treatment was chosen [1]. Covariates are treatment (Trt), 8-week baseline seizure counts (Base), age in years (Age), and V4 which is an indicator variable for the 4th visit.
Random effects are present to take into account inter-individual variability ($b1_j$) and also inter-occasion variability (b_{jk}).

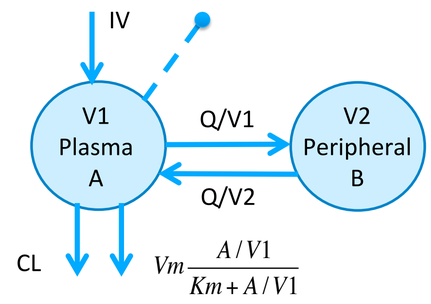
Patient	y_1	y_2	y_3	y_4	Trt	Base	Age
1	5	3	3	3	0	11	31
2	3	5	3	3	0	11	30
3	2	4	0	5	0	6	25
…							
59	1	4	3	2	1	12	37

$$y_{jk} \sim \text{Poisson}\left(m_{jk}\right)$$
$$b1_j \sim N\left(0, \sigma^2_{b1}\right)$$
$$b_{jk} \sim N\left(0, \sigma^2_{b}\right)$$

$$\log\left(m_{jk}\right) = \alpha_0 + \alpha_{Base}\cdot\log\left(\frac{Base_j}{4}\right) + \alpha_{Trt}\cdot Trt_j + \alpha_{BT}\cdot Trt_j\cdot\log\left(\frac{Base_j}{4}\right) + \alpha_{Age}\cdot\log\left(Age_j\right) + \alpha_{V4}\cdot V4_k + b1_j + b_{jk}$$

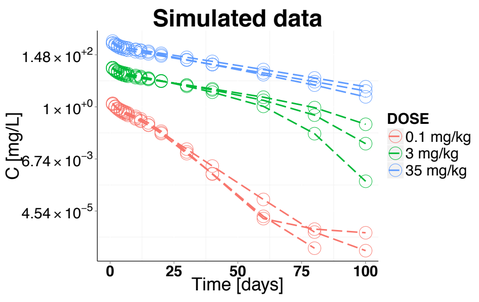
ODE MODEL

A 2-compartment PK ODE model with linear and non-linear elimination, already adopted for a Phase I dose escalation study of a monoclonal antibody for epilepsy, was used [2,3]. Data were generated using the parameter values reported below, via the Simulx function of the R package mlxR. Prior distributions were chosen according to [2].



6 groups of 3 subjects each were simulated with doses=0.01, 0.1, 1, 3, 10, 35 [mg/kg], infusion time=1/24 [day], administered at day 0.

CL_{pop}=0.0045 [L/Kg/day]	σ^2_{CL}=0.0495
$V1_{pop}$=0.0535 [L/Kg]	σ^2_{V1}=0.025
$V2_{pop}$=0.036 [L/Kg]	σ^2_{V2}=0.073
Q=0.0139 [L/Kg/day]	σ^2_{add}=0.0001
Km=0.173 [mg/L]	σ^2_{prop}=0.0107
Vm=0.0037 [mg/Kg/day]	

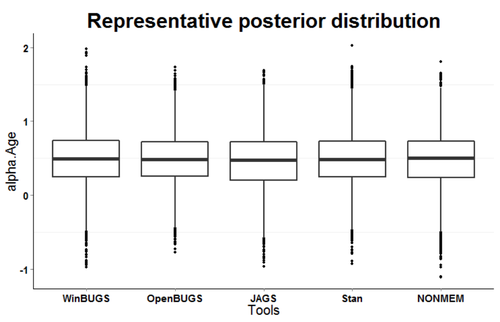


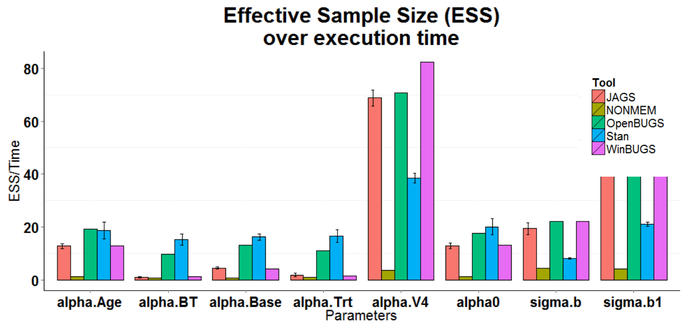
$$y_{ij} = \frac{A_{ij}}{V1_{ij}}\cdot\left(1+\varepsilon_{prop,ij}\right)+\varepsilon_{add,ij} \qquad \varepsilon_{add,ij}\sim N\left(0,\sigma^2_{add}\right) \qquad \varepsilon_{prop,ij}\sim N\left(0,\sigma^2_{prop}\right)$$

$$\log\left(CL_j\right) = \log\left(CL_{pop}\right)+\eta_{CL,j} \qquad \eta_{CL,j}\sim N\left(0,\sigma^2_{CL}\right)$$
$$\log\left(V1_j\right) = \log\left(V1_{pop}\right)+\eta_{V1,j} \qquad \eta_{V1,j}\sim N\left(0,\sigma^2_{V1}\right)$$
$$\log\left(V2_j\right) = \log\left(V2_{pop}\right)+\eta_{V2,j} \qquad \eta_{V2,j}\sim N\left(0,\sigma^2_{V2}\right)$$

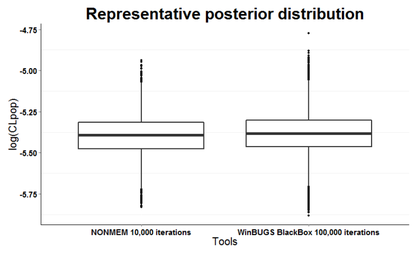
RESULTS.

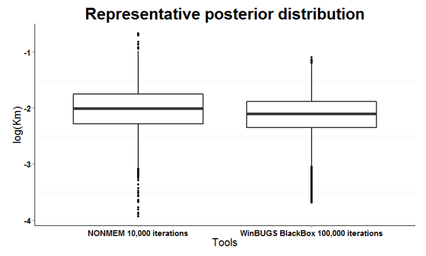
ALGEBRAIC MODEL

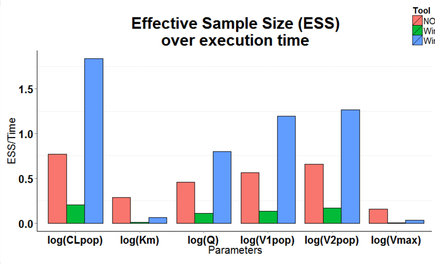


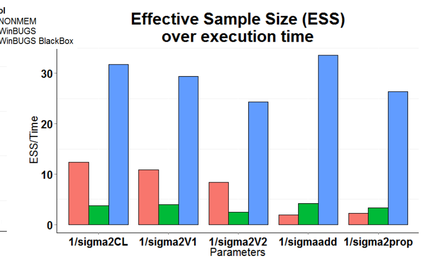


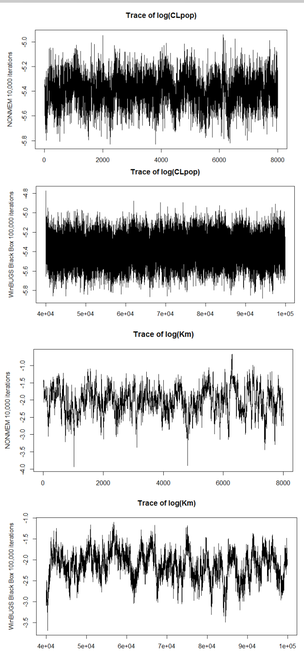
ODE MODEL











CONCLUSIONS.

- Considering the algebraic model, the posterior distributions were comparable for all the tools. OpenBUGS and Stan showed superior performance in terms of ESS/Time.
- Algebraic model implementation in NONMEM required the objective function to be written explicitly, resulting in a less user-friendly model encoding than the other tools. NONMEM also has a limited distribution choice (only Normal and Wishart^{-1} distributions are allowed), thus requiring Gamma-to-Wishart^{-1} parameter transformations.
- The ODE model could be implemented only with NONMEM and WinBUGS (also with BlackBox), since JAGS does not include an ODE solver, OpenBUGS gives errors solving population models with ODEs and Stan could not finish the estimation process.
- NONMEM and WinBUGS with BlackBox showed comparable performance for the ODE model, while WinBUGS alone showed, on average, a considerably lower ESS/Time.

	WinBUGS	NONMEM	Stan	JAGS	OpenBUGS
ALGEBRAIC MODEL	✔	✔	✔✔	✔	✔✔
ODE MODEL	✔	✔	✖	✖	✖

REFERENCES. **[1]** http://www.openbugs.net/Examples/Epil.html.
[2] R.Lledo-Garcia et al. Dose escalation studies for mAb: prior distributions selection and software comparison. Proceedings of the PAGE meeting (2012), June 5-8, Venice, Italy.
[3] F. Strimenopoulou et al. Bayesian non-linear PK modelling applied to dose escalation studies using WinBUGS. Proceedings of the Bayes 2012 meeting, May 9-11, Basel, Switzerland