Evaluation of software tools for Bayesian estimation on population models: an update based on current software versions

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Background. Bayesian modelling based on Markov Chain Monte Carlo (MCMC) methods is acknowledged as a useful instrument in pharmaceutics. This work provides, after 3 years, an updated picture of a previous study [1], in which the performances of several software tools performing Bayesian estimation in a population context were compared in terms of efficiency and reliability of estimates, using as case studies an algebraic model and an ordinary differential equation (ODE) model.

Methods. A total of 12 software tools were considered: WinBUGS 1.4.3 (with BlackBox Component Builder 1.5 and WBdiff interface); Stan 2.17; JAGS 4.3.0; NONMEM 7.4.1 (with BAYES and NUTS). The R code package was used to analyze Markov chains.

The study was conducted on a Windows 10 ASUS desktop PC, with Intel Core i5 3.30Ghz 4 cores and 8GB RAM. The R code package was used to analyze Markov chains.

For each model and tool, the number of iterations in the burn-in and stationary phases was computed based on the Raftery algorithm [2].

Algebraic Model
Poisson count model, describing a clinical trial of an anticonvulsant therapy [3].

Covariates: treatment (Trt), 2-week baseline seizure counts (Base), age (Age), indicator variable for the 4th visit (V4).

Random effects: Inter-Individual (b1j) and Inter-Occasion (b2j) variability.

\[
\log(m_{jk}) = a_0 + a_{\text{Base}} \cdot \log(Base_j/4) + a_{\text{Trt}} \cdot Trt_j + a_{\text{Age}} \cdot \log(Age_j) + a_{\text{V4}} \cdot V4_j + b_{1j} + b_{2j}
\]

Results. Effective Sample Size (ESS) over execution time

ODE Model
2-compartment PK ODE model with linear and non-linear elimination for a Phase I study of a monoclonal antibody for epilepsy [4].

Data: generated via Simulx using the reported parameter values.

Prior distributions: defined according to [4].

Error model: Additional + Proportional.

\[
\begin{align*}
Y \sim & \text{Poisson}(\mu) \\
\log(\mu) = & \log(m_{j}) + \log(CL_{j}) + \log(V_{1,j}) + \log(V_{2,j})
\end{align*}
\]

Conclusions. Algebraic model: the posterior distributions of all the tools were similar to the expected ones.

With count data, NONMEM required the objective function to be written explicitly, resulting in a less user-friendly model encoding. As for ESS/T, NONMEM NUTS and BAYES methods with mu referencing showed better performance with respect to the other tools.

Compared to BAYES, NUTS slightly improved both the efficiency and the estimation results.

ODE model: no tool was able to recover the expected posterior distributions [4] for all model parameters.

In terms of ESS/T, the best performances were obtained with NONMEM NUTS and BAYES methods with mu referencing for fixed effects, whereas WinBUGS showed higher ESS/T for random effects.

Improvements: the NUTS algorithm used in Stan has been successfully implemented as a new feature in NONMEM 7.4.1. In this version, more flexibility has also been given to users in terms of prior distribution choices.

Differently from the previous study, Stan was able to finish the estimation process, even if the estimated posterior distributions are biased and highly skewed.

References.