New Estimation Methods in NONMEM 7: Evaluation of Robustness and Runtimes

UPPSALA UNIVERSITET

Sebastian Ueckert, Åsa M. Johansson, Elodie L. Plan, Andrew C. Hooker, Mats O. Karlsson

Department of Pharmaceutical Biosciences, Uppsala University, Sweden

Background

NONMEM is the most widely used software for population PKPD analyses. The latest version, NONMEM 7 (NM7), includes several new sampling-based estimation algorithms in addition to the classical methods. Besides an evaluation of the accuracy and precision inherent in these methods [See page poster 1922], time to complete estimation and sensitivity with respect to initial estimates (IE) might be critical in practice.

Objective

To investigate the robustness and runtime of the estimation methods available in NM7 for a diverse set of PKPD models.

Methods

Models: Five models representing different types of PKPD data handling were selected for the simulation and estimation (SSE) study:

Model	Fixed Effects	Random Effects
1 Continuous (C)	6	3
2 Binary (B)	2	1
3 Ordered Categorical (OC)	4	3
4 Count (CO)	2	1
5 Repeated Time to Event (RTTE)	2	1

Algorithms: For the categorical data models (2-5), the following estimation methods were investigated: LAPLACE, ITS, SAEM , IMP, IMPMAP, BAYES. For the continuous data model (1), the FOCE instead of the LAPLACE method was used.

All estimation methods were used with their default settings. Furthermore, a convergence test (CTYPE=3) with predefined settings (CINTERVAL=1, CITER=10, CALPHA=0.05) was used for the ITS, IMP and IMPMAP method. For MCMC methods SAEM and BAYES, CINTERVAL was increased to 10 as recommended [2].

SSE Study: Each of the 5 models was used to simulate 100 data sets. All datasets were analyzed twice, (A) starting with initial estimates set to the simulation values and (B) starting at values randomly generated using the CHAIN option. For the latter, fixed effects were sampled from a uniform distribution [Θ-α, Θ-α] (IACCEPT=1); for the random effects, a Wishart density of variance ω_{TRUE} with 20 degrees of freedom was used.

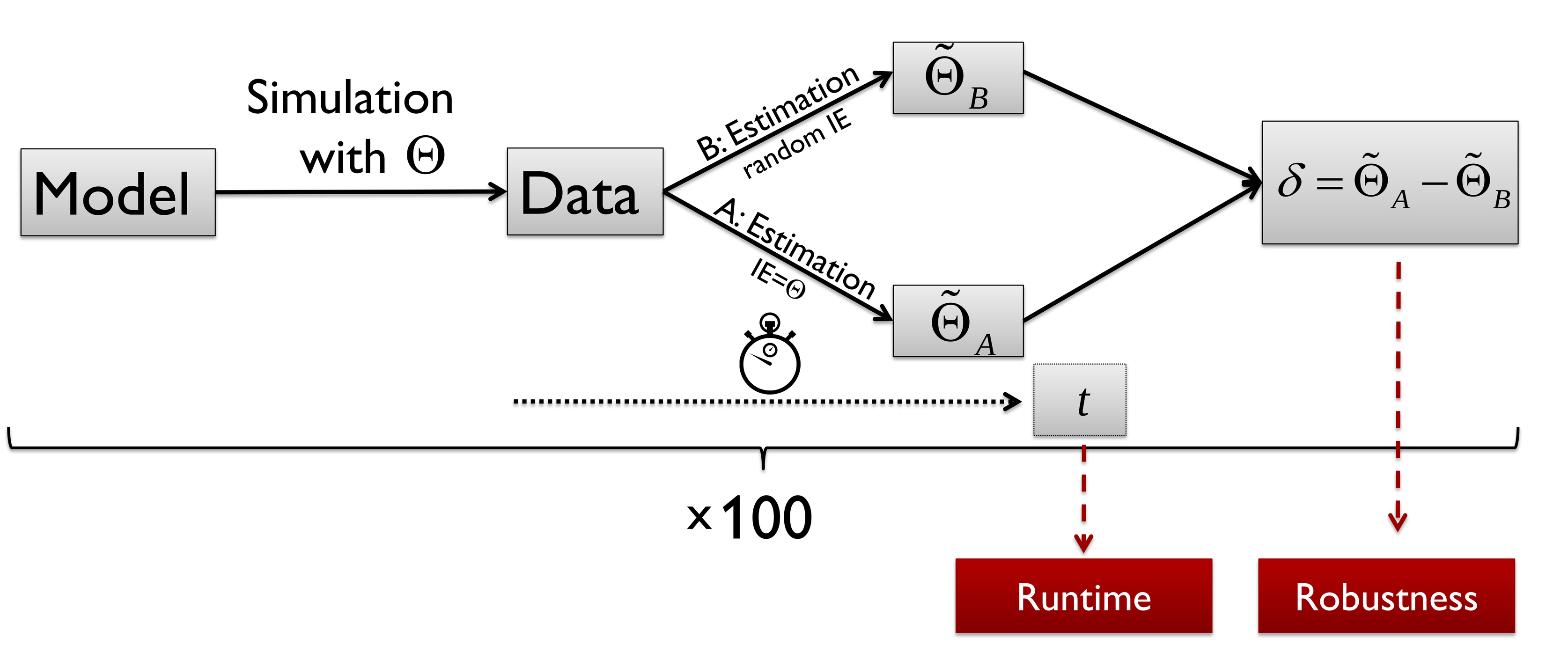

Figure 1: Schematic representation of the simulation and estimation study performed for models 1-5 and all 6 estimation methods.

Robustness: Within a model M, the following procedure was run to calculate the statistic π_{out} for every parameter and estimation algorithm:

(I) construct set $\Delta=\{\delta_1, \delta_2,\ldots,\delta_{600}\}$ of differences δ_i in final parameter estimates between approach (A) and (B) for all algorithms;

(II) determine subset Δ_{out} containing all values δ_i below 5^{th} or above 95^{th} percentile of Δ;

(III) calculate fraction of runs with $\delta_i \in \Delta_{out}$ for each algorithm. Afterwards, mean π_{out} was calculated for all fixed effect and all random effect parameters of M.

An estimation algorithm is considered to be more robust if its mean π_{out} value is low.

Runtimes: NONMEM reported runtimes from all estimations (n=100) of approach (A) were used to calculate average estimation time for each algorithm and each model separately.

Conclusions

Robustness:

- LAPLACE/FOCE most robust (except OC model)
- BAYES least robust

Runtimes:

- LAPLACE/FOCE fastest for all models
- BAYES slowest for all models
- Ranking of SAEM, IMP, IMPMAP differs between models

Results

Robustness

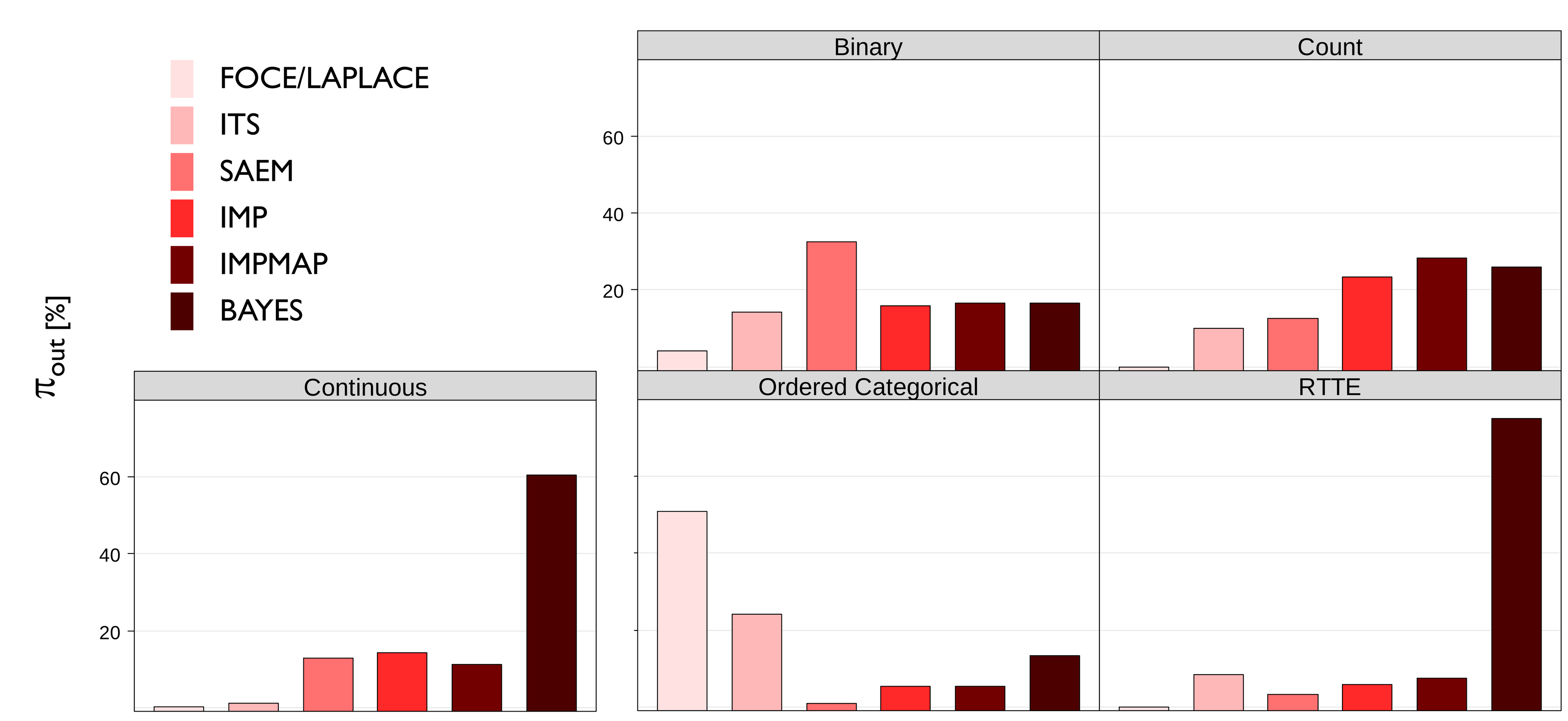

Figure 2: Robustness to changes of initial values for fixed effects.

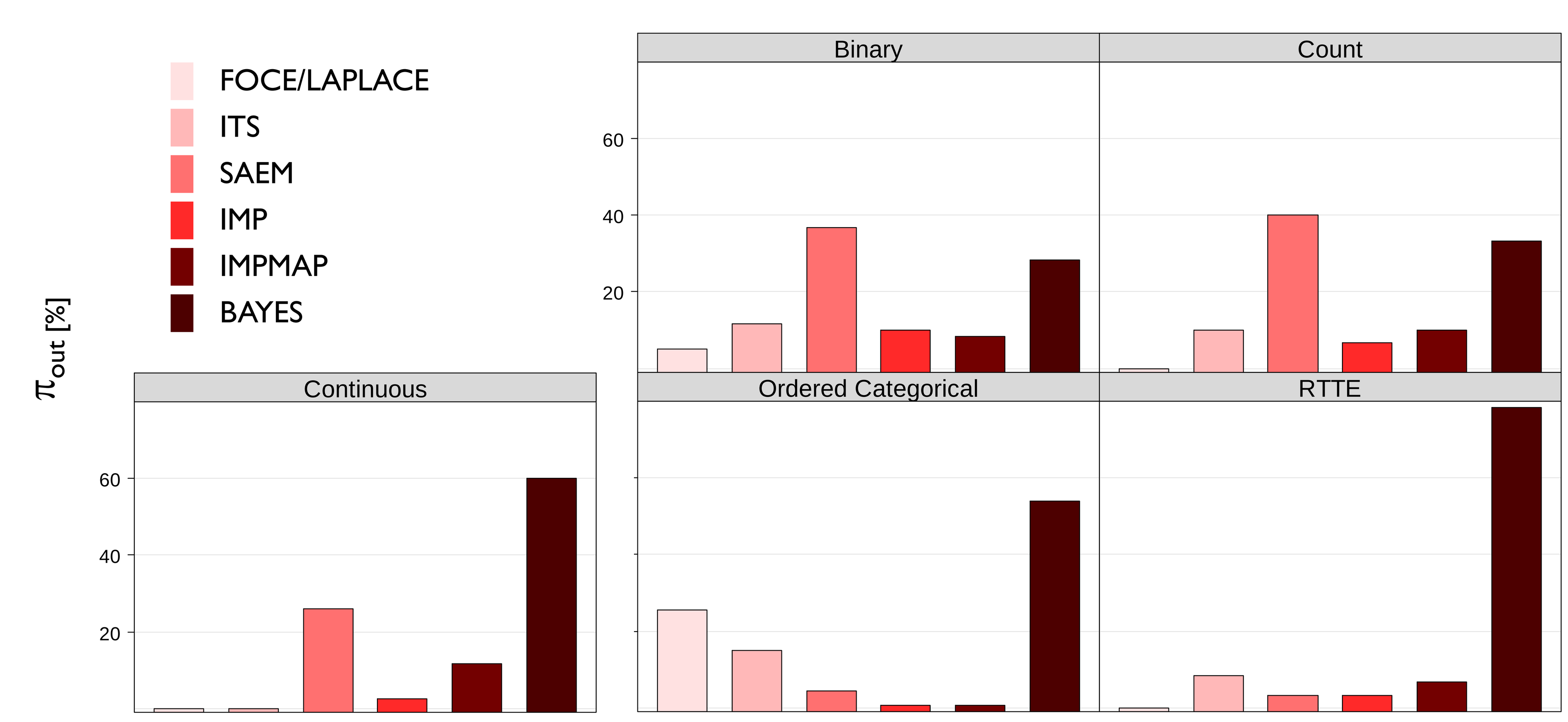

Figure 3: Robustness to changes of initial values for random effects.

Runtimes

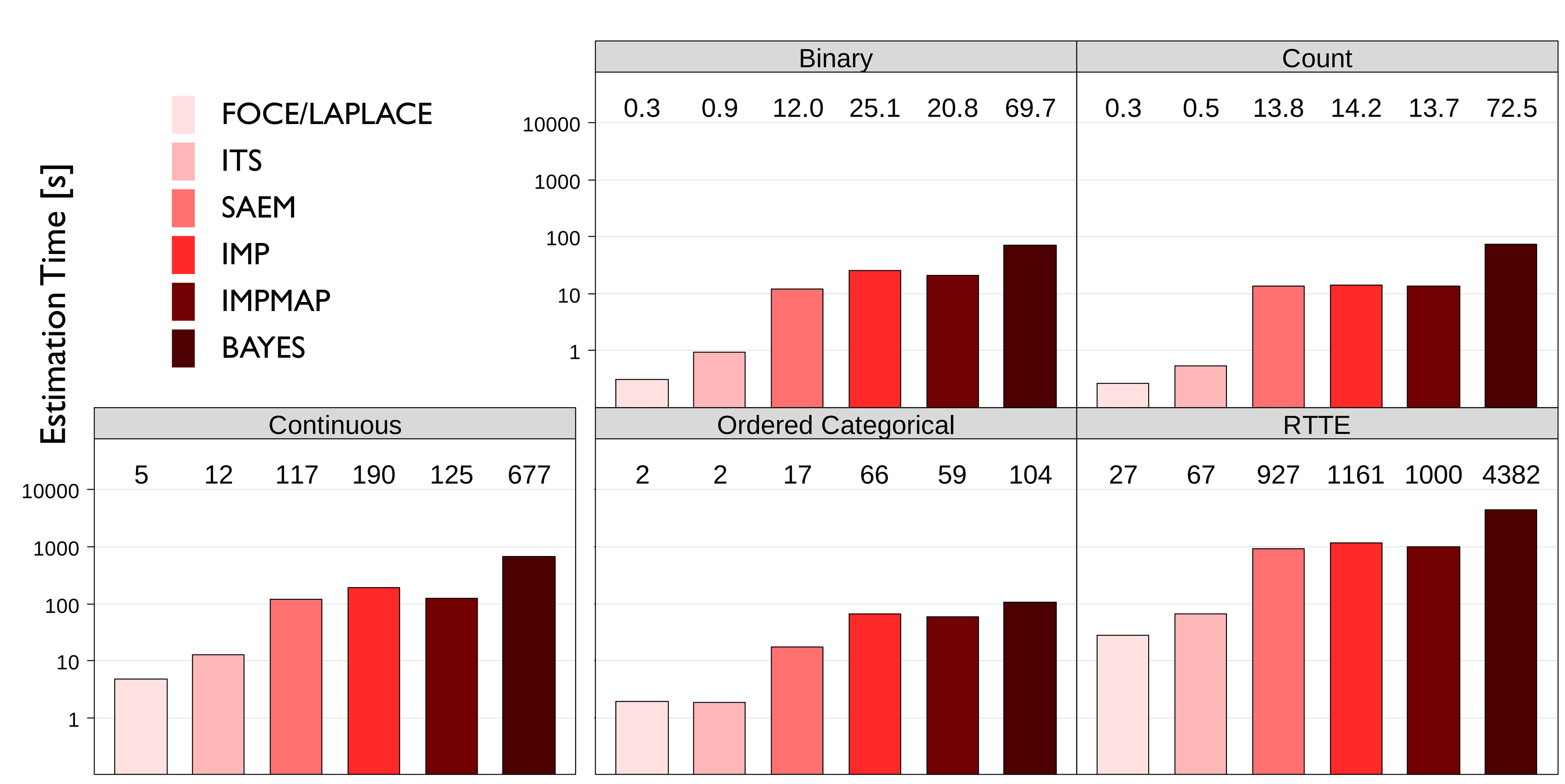

Figure 4: Mean estimation time (n=100) of each algorithm and model type.

[1] Johansson ÅM, Ueckert S, Plan EL, Hooker AC & Karlsson MO: New Estimation Methods in NONMEM 7: Evaluation of Bias and Precision. PAGE 19. 2010.

[2] Bauer RJ. NONMEM users guide; Introduction to NONMEM 7. 2009