# Dose escalation studies: A comparison between NONMEM and a novel Bayesian tool

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## Introduction

In recent years, Bayesian techniques applied to Phase I dose escalation studies have received increasing attention[1,2]. The advantage in adopting Bayesian methods is two-fold: not only parameter uncertainties are fully accounted, but also posterior densities are easily obtained. Both benefits allow a safer escalation to newly enrolled subjects and a more precise individual risk assessment.

## Objectives

Evaluate different modeling approaches and decision making criteria by comparing a traditional NONMEM estimation procedure with a novel Bayesian Escalation Tool (BEsT), featuring both Empirical Bayes and Markov Chain MonteCarlo (MCMC) estimation[3]. Though comparable to NONMEM in most cases, BEsT shows superior performances in some critical but realistic scenarios.

## Methods

### Data

Ten Phase I studies and 20 simulated datasets were analyzed both in NONMEM VI (FOCE interaction, additive intersubject variability and residual error) and BEsT, using a fully Bayesian approach based on MCMC.

### Model assumptions

The dose-response relationship adopted was a linear mixed-effects model using log-transformed doses and exposures (either $C_{max}$ or AUC).

$$y_{ij} = (\vartheta_1 + s_i) + (\vartheta_2 + t_i) d_{ij} + \varepsilon_{ij}$$

with hyperparameters:

$$\sigma_s^2 = Var[s_i] \quad \sigma_t^2 = Var[t_i] \quad \sigma^2 = Var[\varepsilon_{ij}]$$

### BEsT implementation

BEsT is a user-friendly tool based on R and WinBUGS (for the MCMC core). As a result of the estimation process, BEsT produces an extensive report and plots for immediate analysis, both for enrolled subjects and for a generic, untested one:

- **Prediction plot** (Fig. 1, top): individual regression curve with its associated credible limits, together with the predictive distribution at a future dose.
- **Risk plot** (Fig. 1, bottom): probability of exceeding the safety limit as a function of dose. It also displays the critical dose and the future dose risk.

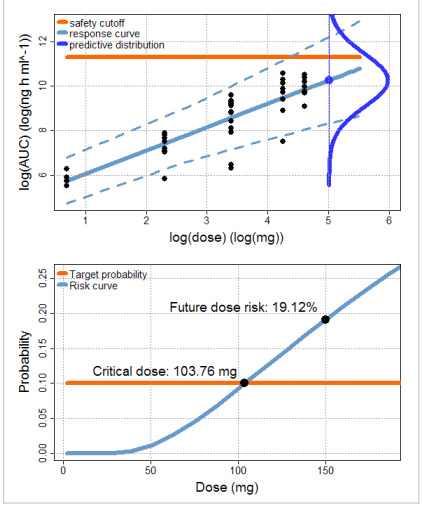


Fig. 1: New subject prediction (top) and risk plot (bottom)

## Results

### Parameter estimates

A comparison benchmark was designed using simulated datasets by estimating parameters with BEsT and NONMEM, then plotting the estimate distributions as boxplots (Fig. 2). True parameter values are denoted by asterisks.

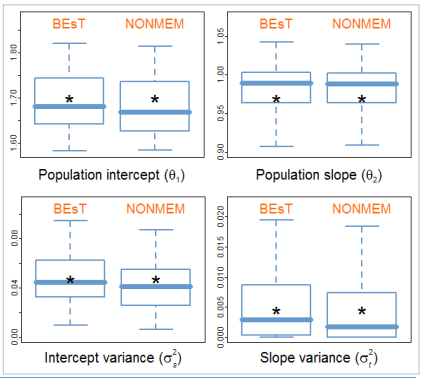


Fig. 2: Parameter estimates comparison

### Predictive performances

Predictive performances of both approaches were assessed, for both real and simulated datasets, in terms of Root Mean Square Error (RMSE), by estimating the model using only a portion of the data and validating it against the other (Fig. 3).

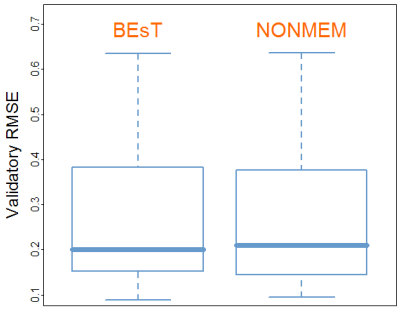


Fig. 3: Predictive RMSE comparison

### Individual risk assessment

BEsT features in terms of individual risk assessment are depicted in Fig. 4. Credible limits are shown along with the regression curve for all subjects, whereas NONMEM only provides the median curve. Not only the interval probability is user-selectable, but also the subject's critical dose is easily obtained.

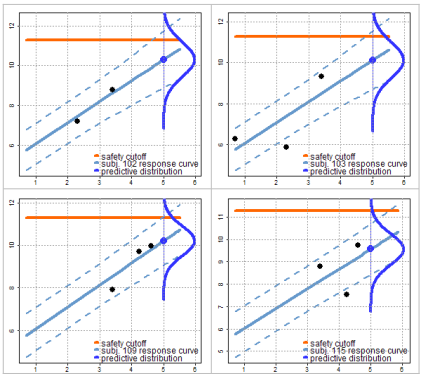


Fig. 4: BEsT's prediction intervals for 4 (real) individuals

## Results (cont'd)

### Prediction limits reliability

Reliability of prediction limits estimation for both approaches was assessed in a small sample-size scenario, i.e. a single cohort of four subjects. Maximum Likelihood estimation, employed by NONMEM, is known to yield downward biased estimates of variance parameters[4], resulting in narrower predictive intervals (Fig. 5).

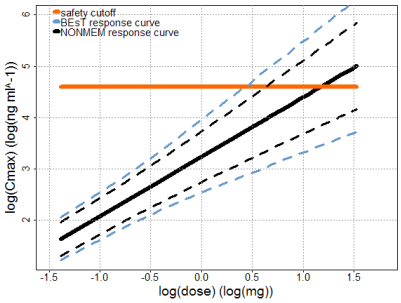


Fig. 5: New subject prediction with BEsT (cyan) and NONMEM (black), small cohort of 4 (real dataset)

Compared to BEsT, NONMEM's systematic underestimation of variance parameters leads to biased future dose risks and critical doses on a new subject in both simulated and real datasets (Fig. 6). Our Bayesian approach properly accounts interindividual variability, by completely propagating it to credible intervals estimation (Tab. 1).

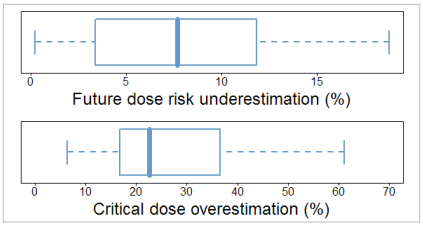


Fig. 6: NONMEM bias assessment in future dose risk and critical dose estimation, relative to BEsT

| Method | Equivalent to | Package | Neglects | Biased |
|---|---|---|---|---|
| Unmarginalized empirical Bayes | Maximum Likelihood | NONMEM | Uncertainty in fixed effects and variance components | yes |
| Empirical Bayes (fixed effects marginalization) | REML | BEsT | Uncertainty in variance components | No |
| Full Bayes (MCMC) | - | BEsT | All uncertainties propagated | No |

Tab. 1: Comparison between different approaches

## Conclusions

- NONMEM, though providing satisfactory point estimates, tends to systematically underestimate prediction intervals if the sample size is small, possibly due to the Maximum Likelihood bias in estimating variance components[3] and the neglecting of fixed effects uncertainty. Also, rigorous individual confidence limits are not easily obtained.
- Conversely, realistic estimates and reliable prediction intervals, suitable for individual risk assessment, were obtained with the new Bayesian tool. Both the higher accuracy and the individual prediction capabilities provided by our Bayesian approach proved to impact positively on the quality of risk assessment during dose escalation.

## References

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