

Impact of Imbalanced Baseline Responses among Dose Levels in the Exposure-Response Analysis by Nonlinear Mixed-Effect Modeling

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INTRODUCTION

- Dose-ranging clinical studies can encounter imbalanced baseline responses among the groups of subjects testing different dose levels of a drug, especially for the cases of no randomization, sequential enrollment, or small number of subjects across the dose levels (e.g., dose-ascending studies conducted in the early-phase clinical development).
- This inter-dose baseline imbalance may complicate the characterization of the dose- or exposure-response (E-R) relationship simply based on the observed data.
- Nonlinear mixed-effect (NLME) modeling is expected in theory to overcome this limitation by appropriately considering the inter-individual variability (IIV) in the data analysis [1].
- However, no dedicated investigation on the parameter estimation performance in the E-R analysis by NLME modeling.

OBJECTIVES

- To evaluate how the inter-dose baseline imbalance impacts the parameter estimation performance in the E-R analysis by NLME modeling.

METHODS

- A stochastic simulation and estimation study was performed using SAS version 9.4 and NONMEM version 7.4.3 for the respective processes.
- Immediate response models with a stimulatory or inhibitory maximum effect (Emax) function of a dose-proportional exposure variable were used for simulating the response data (**Equation 1**). Subjects were evenly allocated to 4 groups of different dose levels including placebo in the following 3 scenarios (**Figure 1**):
 - 1) a subject is randomly allocated to a dose level regardless of the observed baseline response value**
 - 2) and 3) the higher the observed baseline response value for a subject is, the higher or lower the allocated dose level is (i.e., positively or negatively correlated inter-dose baseline imbalance)**
- Accuracy and precision of the parameter estimation by the true models were evaluated and compared among the 3 allocation scenarios. First-order conditional estimation with interaction method was used for the maximum likelihood estimation.
- Alternative models with 1 of the following conditions (B, C, or D) were tested for the estimation for comparison with **the true models (A)**:
 - B) IIV of the baseline response parameter (RBL) is removed (i.e., naive pooled data [NPD] modeling)**
 - C) Estimation of the individual RBLs is conditioned by the observed baseline response values with residual variability correction [2]**
 - D) A nested level of random effect of inter-group variability (IGV) is added on the IIV of RBL by the \$LEVEL functionality [3]**

$$Exposure = (\theta_1 \times e^{\eta_1}) \times Dose$$

$$Response = (\theta_2 \times e^{\eta_2}) \times \left(1 + \frac{\theta_3 \times Exposure}{\theta_4 + Exposure}\right) \times (1 + \varepsilon)$$

Parameter or dependent variable	Value	Estimated
Dose	0 (placebo), 1, 3, 9	No
θ_1 : Population mean of exposure per dose	1	No
ω_1^2 : Variance for IIV of exposure per dose (η_1)	0.04	No
θ_2 : Population mean of RBL	1	Yes
ω_2^2 : Variance for IIV of RBL (η_2)	0.04	Yes
θ_3 : Population mean of Emax	1 if stimulatory; -0.5 if inhibitory	Yes
θ_4 : Population mean of EC50	3	Yes
σ^2 : Variance for residual variability (ε)	0.01	Yes

Equation 1. Model equations and parameters used for the simulation.

EC50 = exposure value to achieve half of Emax.

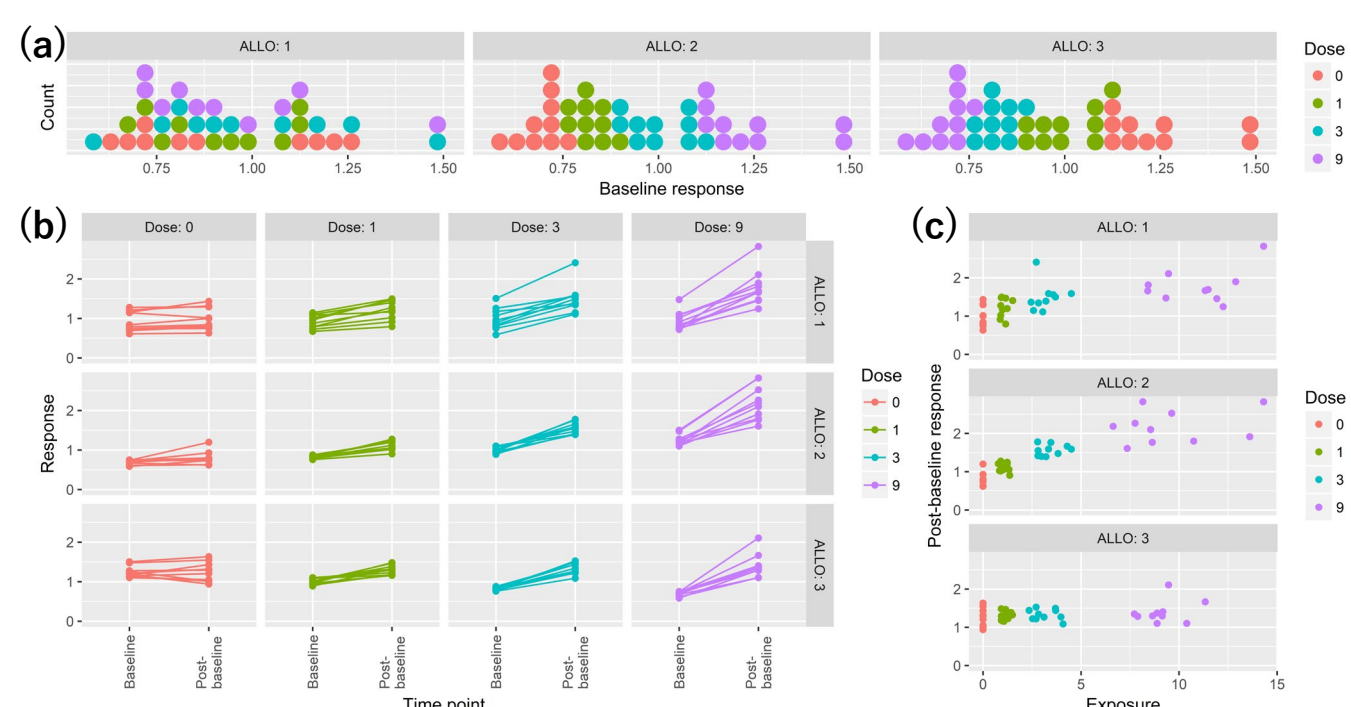


Figure 1. Example set of simulated data applied for the estimation: (a) baseline response and dose level allocation; (b) change of response by drug intervention; (c) post-baseline exposure-response relationship.

ALLO = allocation scenario. Datasets generated by the stimulatory Emax model are presented. Two hundred replicates of the datasets were generated by the stimulatory or inhibitory Emax model each.

RESULTS

- Accuracy and precision of the parameter estimation by **the true models (A)** were comparable among the 3 allocation scenarios (**Figures 2a, 2b**).
- In the presence of inter-dose baseline imbalance, **the NPD modeling (B)** resulted in less accurate estimation of Emax and EC50, which corresponded to higher objective function values (OFVs; higher OFVs occurred even in the absence of inter-dose baseline imbalance), as compared to the true models (**Figures 2a, 2c**).
- The conditioned RBL estimation or IGV addition (C or D)** also tended to result in less accurate estimation of Emax and EC50 in the presence of inter-dose baseline imbalance, while the OFVs were lower (lower OFVs occurred even in the absence of inter-dose baseline imbalance for the case of conditioned RBL estimation), as compared to the true models (**Figures 2a, 2c**).
- Regardless of the presence or absence of inter-dose baseline imbalance, **the NPD modeling or conditioned RBL estimation (B or C)** resulted in less accurate estimation (and less precise estimation for the case of NPD modeling) of the residual variability parameter, as compared to the true models (**Figures 2a, 2b**).
- Sensitivity analysis, which was performed by varying several conditions, supported the validity of these findings. **Use of the LEVWT option on top of the \$LEVEL functionality for the case of IGV addition (D)** had no marked impacts on the accuracy or precision of the parameter estimation or OFV even when the allocation ratio was changed to vary among the dose levels (data not shown).

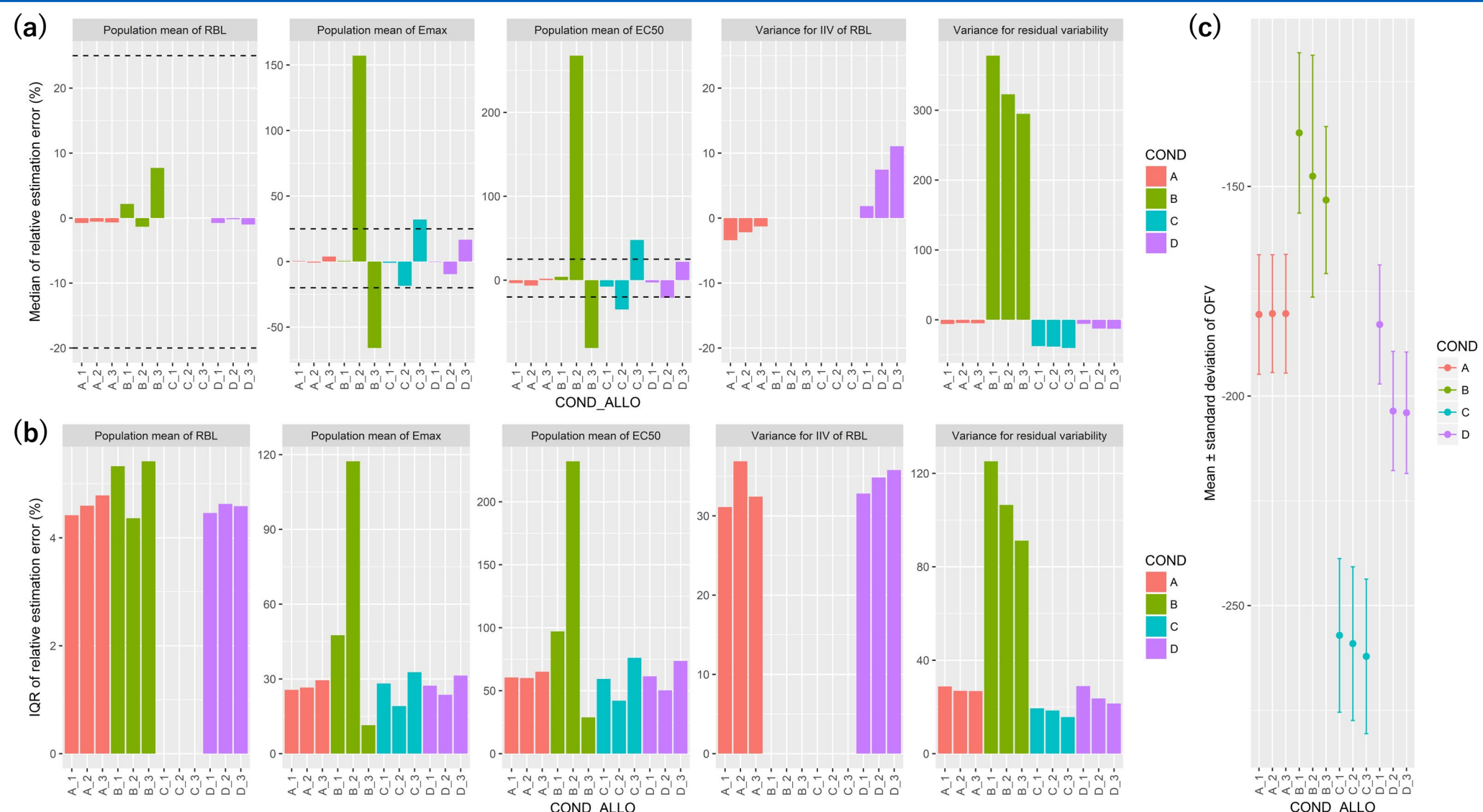


Figure 2. Comparison of (a) accuracy or (b) precision of the parameter estimation or (c) OFV among the estimation conditions and allocation scenarios.

ALLO = allocation scenario; COND = estimation condition; IQR = inter-quartile range. Results for the stimulatory Emax model are presented. Findings for the stimulatory and inhibitory Emax models were consistent. Accuracy of the population mean estimation is benchmarked by -20% and +25% (lower and upper broken lines, respectively). Population mean of RBL was not estimated for COND = C; IIV of RBL was not estimated for COND = B or C.

CONCLUSIONS

- NLME modeling provides stable accuracy and precision of the estimation of Emax model parameters even in the presence of inter-dose baseline imbalance.**
- Careful consideration, not only the OFV comparison, should be made if implementing a modification to the IIV of RBL in relation to the inter-dose baseline imbalance (e.g., what caused the inter-dose baseline imbalance).**
- Further investigations are needed to evaluate the generalizability of these findings from this simple study to more realistically complicated cases (e.g., more IIVs, delayed response models, and discrete response data).**

Conflicts of Interest:

K.Y.: Chugai Pharmaceutical Co., Ltd. for current employment and patents & royalties.
T. S.: Chugai Pharmaceutical Co., Ltd. for current employment, current equity holder, and patents & royalties.

References:

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