Characterizing Bootstrap Model Selection Variability Through an Automated Model Building Approach

Yersultan Mirasbekov[1], Xiaomei Chen[1], Andrew C. Hooker[1], Mats O. Karlsson[1]

[1]Pharmacometrics Group, Department of Pharmacy, Uppsala University, Sweden

Introduction

The development of a population pharmacokinetic (PK) model is a challenging and time-consuming procedure. There are several automatic approaches for model building [1-4]. A fully Automatic Model Development tool (**AMD tool**) has been developed to cover all the components of PK modeling [5]. The AMD tool can potentially automatize model development workflow, and it is integrated into the **Pharmpy/Pharmr** software [6]. The aim of this work is to learn about model selection variability and its consequences using the AMD tool and its model selection modules [5-8].

Methods

The AMD tool was applied to 4 clinical PK datasets of intravenously administered drugs of Daunorubicin, Gentamicin, Pefloxacin, and Tobramycin [9-11]. These datasets were used to generate 10 bootstrapped datasets each. The AMD tool (Pharmr version 0.78) was applied with the 3 modules for the model selection in the following order:

- Structural model
- Inter-Individual Variability (IIV) model
- Residual Unexplained Variability (RUV) model

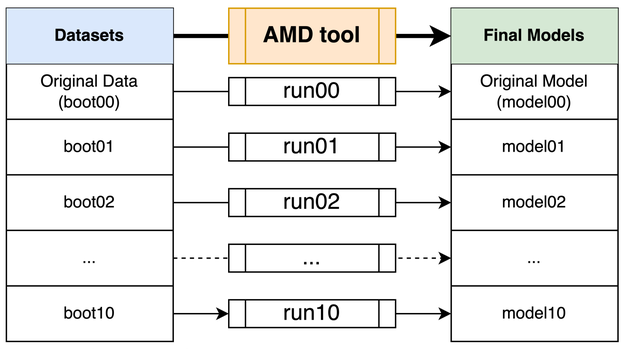

Figure 1. A workflow of generating final models from the original dataset and bootstrapped datasets using the AMD tool.

Objectives

Assessing the effect of the variability of input data on the selection of the final model:

Part I to compare the final models from the original data and bootstrap datasets.

Part II to learn about parameter variability in the presence and absence of model selection variability.

Part III to assess bootstrap-generated models on the original dataset.

Results

Part I

The goodness of fit was getting better (lower BIC) after each module. The variability of bootstrap-generated models was evaluated by the number of differences in selected models compared to the original model. The final models based on bootstrap datasets usually had at least one difference in model selection.

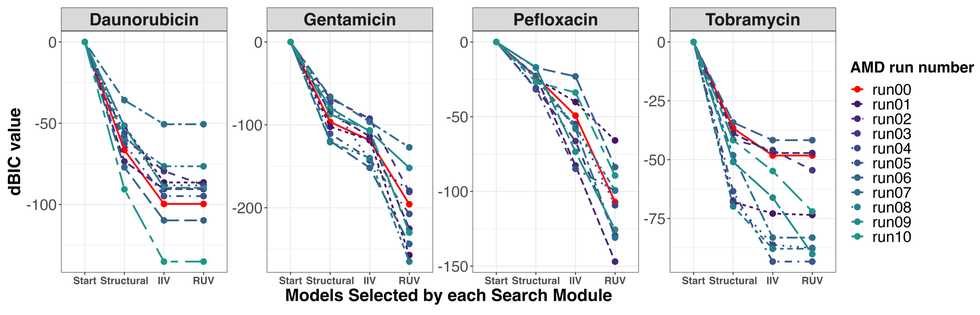

Figure 2. The change of goodness of fit (dBIC value) after each AMD module. dBIC values were calculated relative to the BIC value of the starting model.

Categorical Scoring of Differences

model01	model02	model03	model04	model05	model06	model07	model08	model09	model10	Mean	
1	1	2	1	1	1	1	1	1	1	1.1	Daunorubicin
1	0	3	1	1	0	1	1	3	2	1.3	Gentamicin
2	1	0	1	2	1	1	2	2	2	1.3	Pefloxacin
3	2	2	2	2	1	1	1	3	1	1.7	Tobramycin

Figure 3. A categorical scoring of differences of bootstrap-generated final models (model01-model10) in comparison to the final model from original data (model00).

When modules were evaluated separately, the consistency (the cases when the bootstrap was the same model as the original model) of the Structural model selection was higher than IIV and RUV modules.

Table 1. Evaluation of similarity at each AMD module. The percentage similarity was defined by the percentage of having the same selected model as in the original model for bootstrap-generated models (out of 10) at each module separately.

	Percentage Similarity AMD Modules (%)		
Datasets:	**Structural**	**IIV**	**RUV**
Daunorubicin	100	0	90
Gentamicin	80	70	30
Pefloxacin	100	40	20
Tobramycin	60	10	50
Average:	**85**	**30**	**47.5**

Part II

The coefficient of variability (CV) of parameter estimates from 10 bootstrap results was calculated, and the estimation of typical values of the clearance (CL) showed a similar CV regardless of the inclusion of model selection or not. For the typical value of the volume of distribution (Vss), CV in Tobramycin and Gentamicin datasets was considerably higher with model selection variability than without.

Table 2. Coefficient of variability for estimation of Clearance (CL) and Volume of Distribution (Vss). Parameters were estimated by the original model (model0) or by all bootstrap-generated models (model1-10) using bootstrap datasets. The original model was additionally assessed with 100 bootstrap datasets.

Parameter	Dataset	Model	Coefficient of Variability (%)			
			Daunorubicin	**Gentamicin**	**Pefloxacin**	**Tobramycin**
CL	boot(01-10)	model(01-10)	17.9	3.0	7	10.4
	boot(01-100)	model00	21.1	2.7	6.3	7.8
	boot(01-100)	model00	20.2	3.0	7.6	6.1
Vss	boot(01-10)	model(01-10)	20.8	63.8	19.2	28.4
	boot(01-10)	model00	23.8	5.6	11	12.7
	boot(01-100)	model00	25.1	19.6	14.5	13.6

Part III

The original model and bootstrap-generated models were compared in terms of BIC by parameter estimation of models using the original dataset. When bootstrap-generated models were applied to original data, with re-estimation, they were found to improve on the original model in 3 cases out of 40, all for the Tobramycin dataset (the largest decrease in BIC was 11.1).

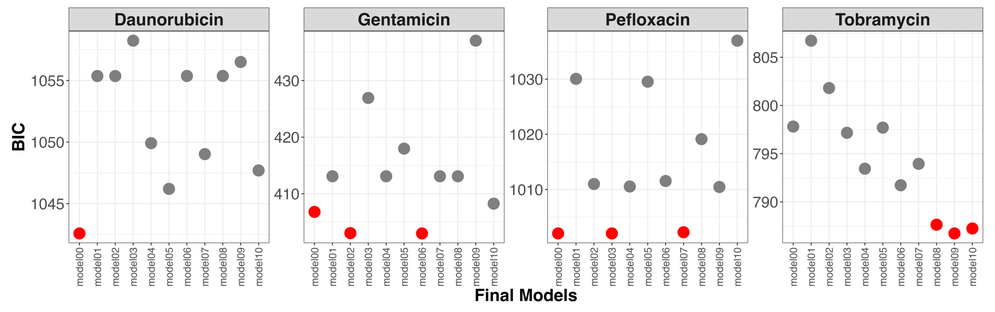

Figure 4. The comparison of the goodness of fit by parameter estimation using the original dataset for the original model (model00) and bootstrap-generated models (model01-model10)

Conclusions

Part I Variability in the model selection of AMD modules

- lowest: structural model selection (the first in a decision tree)
- highest: IIV model selection.

Part II Effect of model selection on overall parameter uncertainty

- varied between parameters: low for CL and high for Vss.

Part III Bootstrap-generated models

- lower BIC when compared to the original model for the Tobramycin dataset.

The pipeline of generating final models from bootstrapped datasets can serve multiple purposes in the understanding of model development and the final model properties.

List of References

1. Jonsson, E. N., & Karlsson, M. O. (1998). Automated covariate model building within NONMEM. *Pharmaceutical research*, 15(9), 1463-1468.
2. Sale, M., & Sherer, E. A. (2015). A genetic algorithm based global search strategy for population pharmacokinetic/pharmacodynamic model selection. *British journal of clinical pharmacology*, 79(1), 28-39.
3. Prague, M., & Lavielle, M. (2022). SAMBA: A novel method for fast automatic model building in nonlinear mixed-effects models. *CPT: Pharmacometrics & Systems Pharmacology*, 11(2), 161-172.
4. Ayral, G., Si Abdallah, J. F., Magnard, C., & Chauvin, J. (2021). A novel method based on unbiased correlations tests for covariate selection in nonlinear mixed effects models: The COSSAC approach. *CPT: pharmacometrics & systems pharmacology*, 10(4), 318-329.
5. Chen, X., Hamdan, A., Wang, S., Yang, T., Nordgren, R., Belin, S., Huang, Z., Carter, S. J., Buatois, S., Abrantes, J. A., Hooker, A. C. & Karlsson, M. O. "Development of a tool for fully automatic model development (AMD)". *PAGE*, 30:10091 www.page-meeting.org/?abstract=10091.
6. Nordgren, R., Belin, S., Yngman, G., Huang, Z., Carter, S. J., Chen, X., Qutishat, O., Hamdan, A., Wang, S., Yang, T., Assawasuwannakit, P., Buatois, S., Abrantes, J. A., Hooker, A. C. & Karlsson, M. O. (2022). Pharmpy: a versatile open-source library for pharmacometrics. *PAGE*, 30:10096. www.page-meeting.org/default.asp?abstract=10096
7. Delattre, M., Lavielle, M., & Poursat, M. A. (2014). A note on BIC in mixed-effects models.
8. Ibrahim, M., Nordgren, R., Kjellsson, M. C., & Karlsson, M. O. (2018). Model-based residual post-processing for residual model identification. *The AAPS Journal*, 20(5), 1-9.
9. Aarons, L., Vozeh, S., Wenk, M., Weiss, P. H., & Follath, F. (1989). Population pharmacokinetics of tobramycin. *British journal of clinical pharmacology*, 28(3), 305-314.
10. Wählby, U., Thomson, A. H., Milligan, P. A., & Karlsson, M. O. (2004). Models for time-varying covariates in population pharmacokinetic-pharmacodynamic analysis. *British journal of clinical pharmacology*, 58(4), 367-377.
11. Bogason, A., Quartino, A. L., Lafolie, P., Masquelier, M., Karlsson, M. O., Paul, C., ... & Vitols, S. (2011). Inverse relationship between leukaemic cell burden and plasma concentrations of daunorubicin in patients with acute myeloid leukaemia. *British journal of clinical pharmacology*, 71(4), 514-521.

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