

Comparison of PK models using normal and log-transformed scale data

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Introduction

Background

- Pharmacometric modelers typically either choose normal scale or log-transformed data based on preference or subjective criteria.
- The dynamic transform both sides (dTBS) tool allow comparisons of the OFV between the two options [1].

Aim

Compare performance on the use of normal scaled data and log-transformed data at different stages of the automatic model development tool in PharmPy (AMD) [2].

Methods

Data

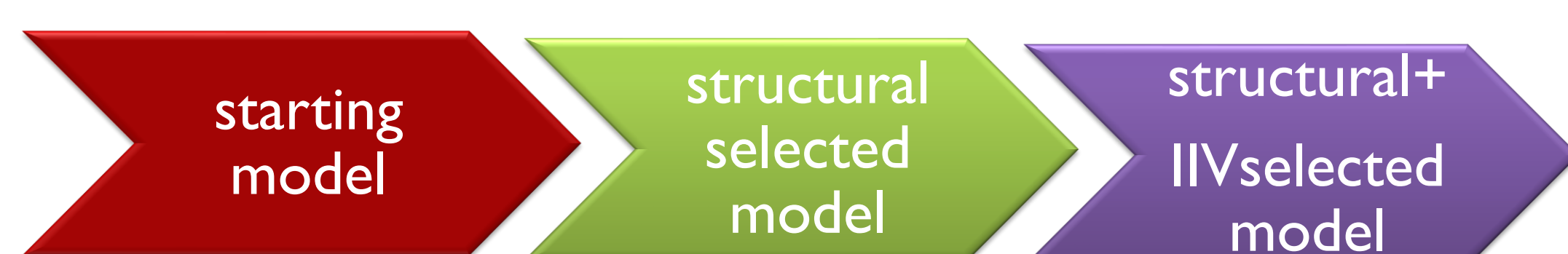
- Five oral drugs (moxonidine, desmopressin, warfarin, lopinavir, melagatran) and five *i.v.* drugs (gentamicin, tobramycin, daunorubicin, factor VIII, pefloxacin) were evaluated by the AMD tool in PharmPy[2].

Process

- Models were transformed with the dTBS tool in PsN [3]. The example code is shown as below:

```
execute example.mod -dTBS -TBS_lambda="0 FIX" -TBS_zeta="0 FIX"
```

- The AMD milestone models with untransformed and transformed data were compared using BIC[4].



Milestone models followed SIR path of AMD process

- The milestone models were also built with the log scale datasets which were transformed manually and compared with the current model structure and IIV selection in AMD. The BIC was used to evaluate models in the process.

References

- [1] Dosne A, Bergstrand M, Karlsson MO. A strategy for residual error modeling incorporating scedasticity of variance and distribution shape. J Pharmacokinet Pharmacodyn. 2015;43(2):137–51. <https://doi.org/10.1007/s10928-015-9460-y>.
- [2] Xiaomei Chen, Alzahra Hamdan, Shijun Wang, Tianwu Yang, Rikard Nordgren, Stella Belin, Zhe Huang, Simon J. Carter, Simon Buatois, João A. Abrantes, Andrew C. Hooker, Mats O. Karlsson, Development of a tool for fully automatic model development (AMD), PAGE 2022
- [3] Lindbom L, Pihlgren P, Jonsson EN. PsN-toolkit—a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Prog Biomed. 2005;79(3):241–57. <https://doi.org/10.1016/j.cmpb.2005.04.005>.
- [4] Delattre M, Lavielle M, Poursat M-A. A note on BIC in mixed-effects models. Electronic journal of statistics 8 (1), 456-475.

Results

The evaluated BIC for all milestone models with dTBS transformation is shown in Figure 1.

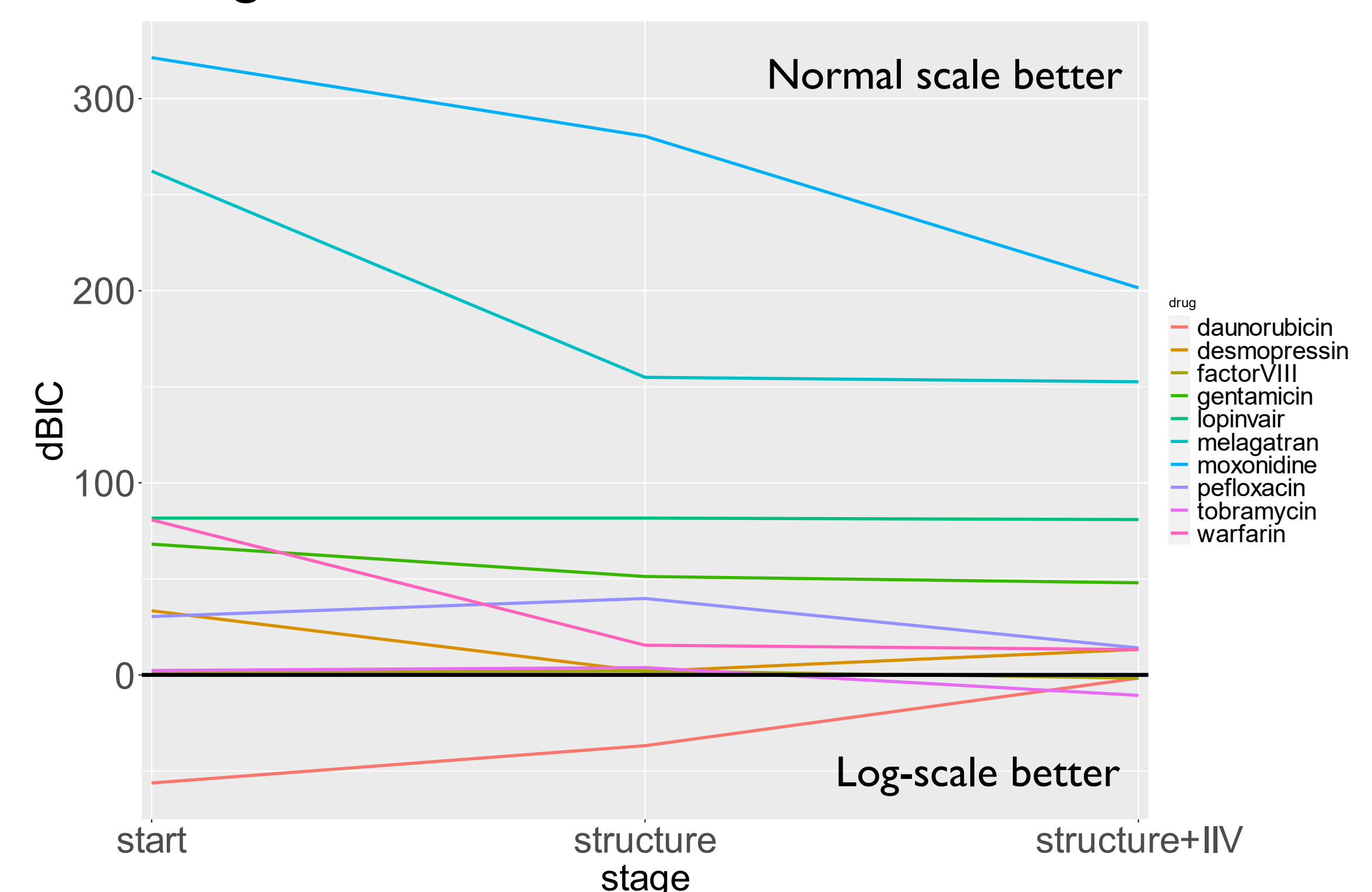


Figure 1. The results of dTBS check for milestone models of 10 drugs at all stages of AMD.
*dBIC = BIC_dTBS - BIC_original

The compared BIC for models with different data scales after model development with log-scale datasets is given in Figure 2.

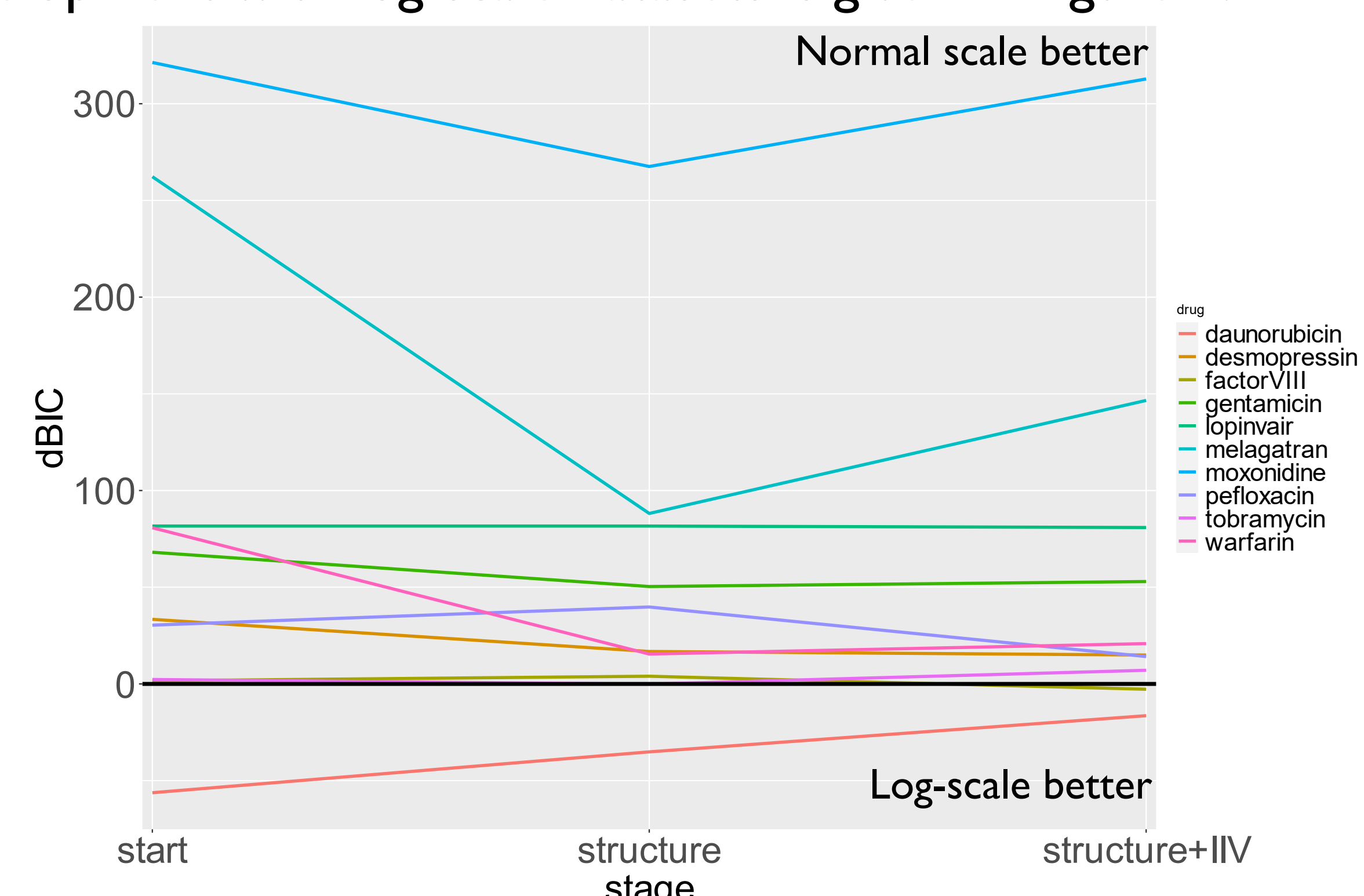
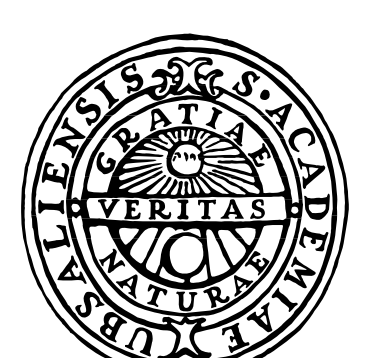


Figure 2. The results of milestone models with two different dataset scales in AMD.
*dBIC = BIC_log - BIC_normal

- For 7/10 drugs – same structural model chosen regardless of data transformation.
- For 4/7 drugs – same IIV model chosen regardless of data transformation.

Conclusions

- For most datasets, models had higher likelihood using normal scale data compared to log-transformed data even when log-transformed data was used for model development.
- Model selection was similar for the two transformations.
- It may suffice to compare the relative performance of normal scale and log-transformed data at starting point during the model building scheme.



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