Performance evaluation of the full Automatic Model Development (AMD) tool when the true model is known

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Introduction

- The **Automatic Model Development (AMD) tool** in **Pharmpy** is an open source tool for automatic population PK model building [1, 2]
- Starting from a PK dataset, the AMD tool automatically creates and fits multiple candidate models using NONMEM, and selects the best model based on predefined criteria
- We assessed the performance of the AMD tool with multiple scenarios of simulated datasets where the true models were known

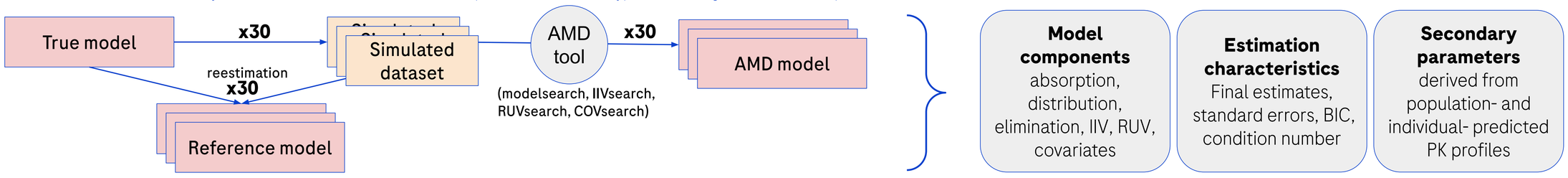
Objective

- To assess the performance of the AMD tool using simulated rich population PK datasets in a clinical drug development context

Methods

- A previously published PK model was adjusted to create **10 true models (scenarios)** used for simulations [3]. All models had 2 distribution compartments (CMT) and differed in: (i) **absorption model complexity** (first order [FO] absorption with or without delay [3 transit CMT], slow or rapid absorption), (ii) **elimination type** ([FO], Michaelis-Menten [MM], or mixed [MIX-FO-MM]), (iii) **complexity of inter-individual variability (IIV) structures**, (iv) **magnitude of proportional residual unexplained variability (RUV)**, and (v) presence/absence of **food effect** on absorption
- For the simulations, a **phase I study design** was assumed: a single ascending dose study (6 cohorts of 6 IDs with ~24 samples) and a multiple ascending dose study (4 cohorts of 9 IDs with ~38 samples)
- From each **true model** 30 dataset replicates were simulated. Each dataset replicate was used as an input for the AMD tool, resulting in 30 final **AMD models** per scenario. True models were also fitted to simulated datasets, referred to as **reference models**. Three types of models were compared. The same framework, as shown in Figure 1, was applied for all scenarios.
- The workflow was automated using pharmr (0.86.0), assemblerr (0.1.2) and qpNCA (1.1.6) in R, and NONMEM (7.5.1) in the validated environment Improve

Figure 1. Automated simulation and analysis framework for one scenario, model components assessed and types of metrics gathered for each replicate of one scenario



Results

- The AMD tool successfully built models for all simulated scenarios
- For each scenario, results were summarized across the 30 replicates, as illustrated in Figure 2, Figure 3, and Table 1, for the highlighted scenario (slow and complex absorption)

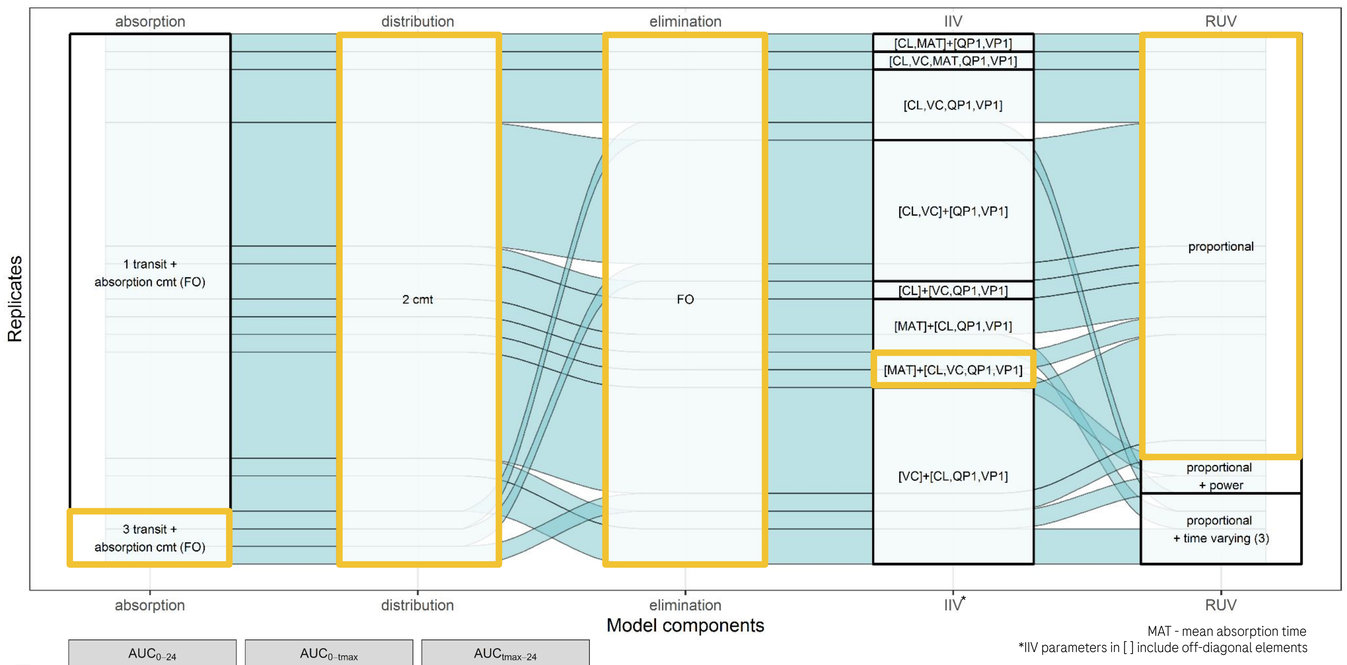
- The AMD tool selected **structural models** that were mostly similar to the true model (e.g. Figure 2)
  - True disposition model was identified for all scenarios and replicates
  - True elimination model was identified for all replicates in FO or MM scenarios, and for most replicates in MIX-FO-MM elimination scenarios
  - In the scenario with rapid complex absorption, selected absorption models were simplified, in scenarios with non-linear elimination and simple FO absorption, the absorption models exhibited substantial variation, while in the rest of the scenarios true absorption was mostly identified
- AMD tool selected **IIV models** that were mostly different from the true structure (e.g. Figure 2), however:
  - Secondary PK parameters derived from the reference models and the AMD models, deviated from the true parameters in a similar manner (e.g. Figure 3)
  - In most scenarios and replicates, for most parameters, the median difference between AMD and reference parameters values was <0.1% (interquartile range of <1.0%) (Equation 3)
- The **true RUV model** was identified in most scenarios
- Increase in RUV (from 26.4% to 50.0%) did not affect the ability of the tool to find models with appropriate PK profile predictions
- The **BIC** of AMD models tended to be similar to the BIC of reference models (e.g. median and range difference of -2 [-8,10] for the highlighted scenario)
- AMD models mostly had reasonable condition numbers, parameter estimates and precision (e.g. Table 1)

Table 1. Comparison of estimation characteristics between AMD models and reference models for the scenario with slow and complex absorption

	AMD models	Reference models
Minimization successful	29 / 30	27 / 30
Condition number <1000	28 / 28*	11 / 11*
RSE for fixed parameters >20%	8 / 28*	4 / 11*
RSE for random parameters >40%	10 / 28*	11 / 11*

*number considering runs with successful covariance step

Figure 2. Alluvial plot for the components of the final AMD models for the scenario with slow and complex absorption. Each longitudinal band represents one AMD model (30 replicates in total). Each band passes through different transversal rectangles representing different model components selected by the AMD tool. Bands with the same model components are merged together. Highlighted boxes represent the true model components.



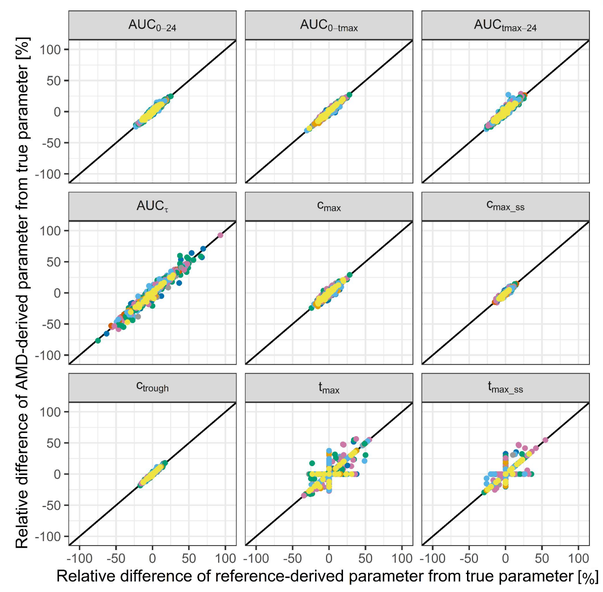


Figure 3. **Deviation of AMD-** (y-axis) **and reference-** (x-axis) derived **individual-predicted** secondary parameters from true parameters for the scenario with slow and complex absorption. The figure includes results for all replicates pooled together. Each dot represents one individual parameter.

Most of the points, regardless of the IIV component, lie on the **unity line**, indicating that **AMD parameters are as close to true parameters as reference parameters**.

AMD model IIV component*
- [CL,MAT]+[QP1,VP1]
- [CL,VC,MAT,QP1,VP1]
- [CL,VC,QP1,VP1]
- [CL,VC]+[QP1,VP1]
- [CL]+[VC,QP1,VP1]
- [MAT]+[CL,QP1,VP1]
- [MAT]+[CL,VC,QP1,VP1]
- [VC]+[CL,QP1,VP1]

Equation 1. Y-axis of figure 3

$$AMD_{true}\ difference = \frac{AMD_{parameter} - true_{parameter}}{true_{parameter}} \cdot 100\%$$

Equation 2. X-axis of figure 3

$$reference_{true}\ difference = \frac{reference_{parameter} - true_{parameter}}{true_{parameter}} \cdot 100\%$$

Equation 3. $$AMD_{reference}\ difference = \frac{AMD_{parameter} - reference_{parameter}}{reference_{parameter}} \cdot 100\%$$

*IIV parameters in [ ] include off-diagonal elements

Conclusion

- **The AMD tool generates models that describe common datasets well** and from which **accurate population and individual predicted PK profiles** are derived
- This work showcases the **usefulness** of the AMD tool in an automated modelling and simulation environment in a drug development setting [4]

References

[1] Chen X, *et al.* PAGE 30 (2022) Abstr 10091 [www.page-meeting.org/?abstract=10091]
[2] AMD tool [Internet]. https://pharmpy.github.io. [cited 2023 Mar 7]
[3] Cosson V, *et al.* (2018), doi:10.1111/cts.12566
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