

Evaluation of automated model development workflows for population pharmacokinetic models

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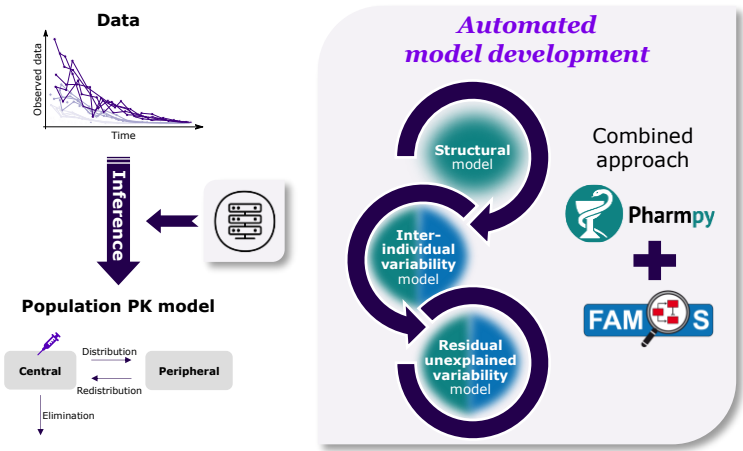


INTRODUCTION

- PharmPy**^{1,2} implements an automated model development (AMD) workflow to identify the optimal population pharmacokinetic model.
- FAMoS**^{3,4} performs automated model selection aimed at analyzing complex and large systems biology systems in a flexible, efficient, and dynamical manner, employing the classical forward and backward search, and a novel swap search algorithm.

Objective

- Evaluate the performance of the **combined FAMoS-PharmPy** approach with synthetic and real datasets.



METHODS

Model structure for synthetic datasets

- 2-compartment disposition with
 - linear clearance or combined with target-mediated drug disposition,
 - first-order absorption or intravenous administration.
- 30% inter-individual variability in clearance.
- 10% proportional residual error.
- Same PK parameter values for all models.

Two real-data examples

- M9: intravenous, multiple ascending dose
- M10: intravenous, single ascending dose

Benchmark models

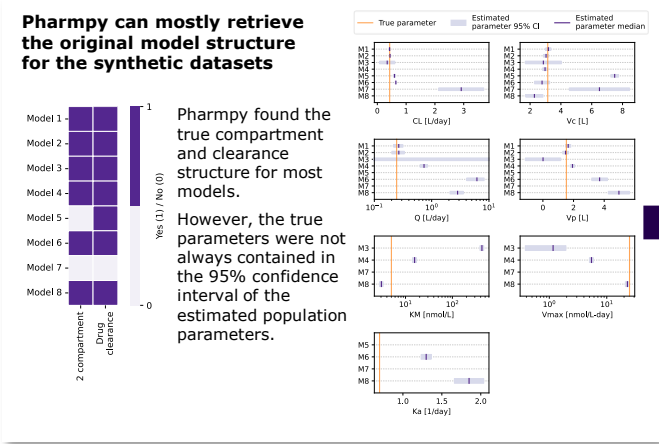
	Synthetic data	Administration	Drug clearance	Data sampling
M1	✓	Intravenous	Linear	Rich
M2	✓	Intravenous	Linear	Sparse
M3	✓	Intravenous	TMDD	Rich
M4	✓	Intravenous	TMDD	Sparse
M5	✓	FO absorption	Linear	Rich
M6	✓	FO absorption	Linear	Sparse
M7	✓	FO absorption	TMDD	Rich
M8	✓	FO absorption	TMDD	Sparse
M9	✗	Intravenous	Unknown	-
M10	✗	Intravenous	Unknown	-

FO, first-order; TMDD, target-mediated drug disposition

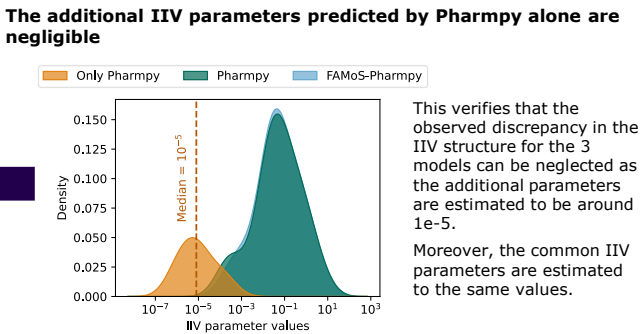
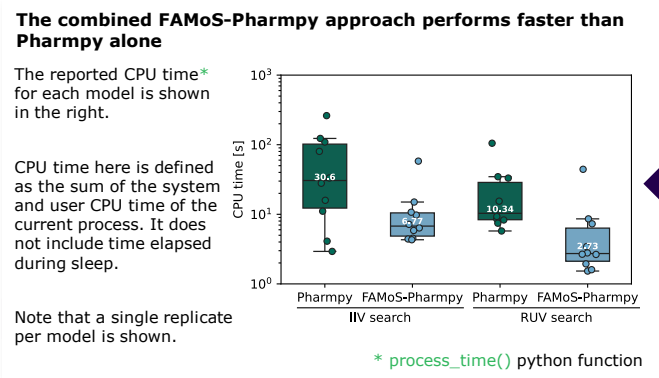
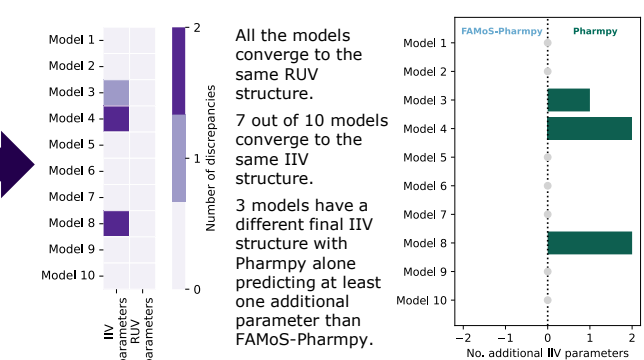
Data sampling for synthetic datasets

- Richly sampled profiles
 - 5 Q2W single doses of 10, 30, 60 and 120 mg,
 - 20 subjects,
 - every hour at a random time point.
- Sparse sampled profiles
 - 10 Q2W doses of 120 mg,
 - 200 subjects,
 - 4 random time points at the first and last dose.

RESULTS



The combined FAMoS-PharmPy can find the same IIV and RUV structures as PharmPy alone



Conclusions

- FAMoS** has the potential to **enhance** the current AMD search workflow of **PharmPy**.
- The results suggest that FAMoS provide a **more efficient** workflow with **identical modeling conclusions**.
- Extensions, such as covariate model development, must be explored.
- Integrating methods from the **systems biology** field can **boost pharmacometrics** workflows.

REFERENCES

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