Automatic Development of Pharmacokinetic Structural Models – Pharmpy Modelsearch Tool

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Introduction

The current development strategy of population pharmacokinetic models is a complex and iterative process that is manually performed. Such a strategy is time-demanding, subjective, and dependent on the modelers' experience. In this work, we present a novel model building tool [1], as part of the **Pharmpy** [2,3] software package in python and its R wrapper package **pharmr**, that automates the development process of pharmacokinetic structural models.

Methods

Modelsearch is a Pharmpy tool that searches for the best structural model using an exhaustive stepwise search algorithm and given a dataset, a starting model and a pre-specified model search space.

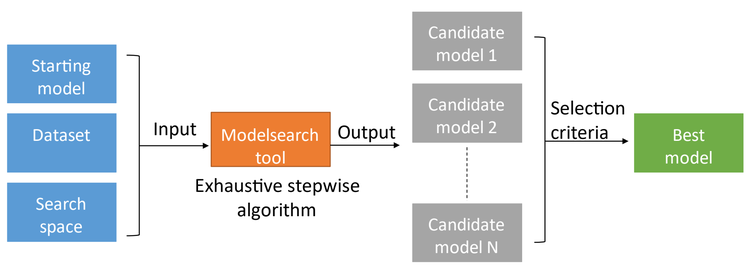

Figure 1. The workflow of the Modelsearch tool.

- The **search space** is a list of structural model features to be considered during the search and can include different models that describe the absorption delay, absorption, distribution, and elimination of the administered drug.
- The **exhaustive stepwise algorithm** tests all possible combinations of model features in a stepwise manner by adding model features one by one in each step. As a result, some models are repeatedly estimated from different orders of adding model features and hence different initial values. This increases the robustness of the final model selection.

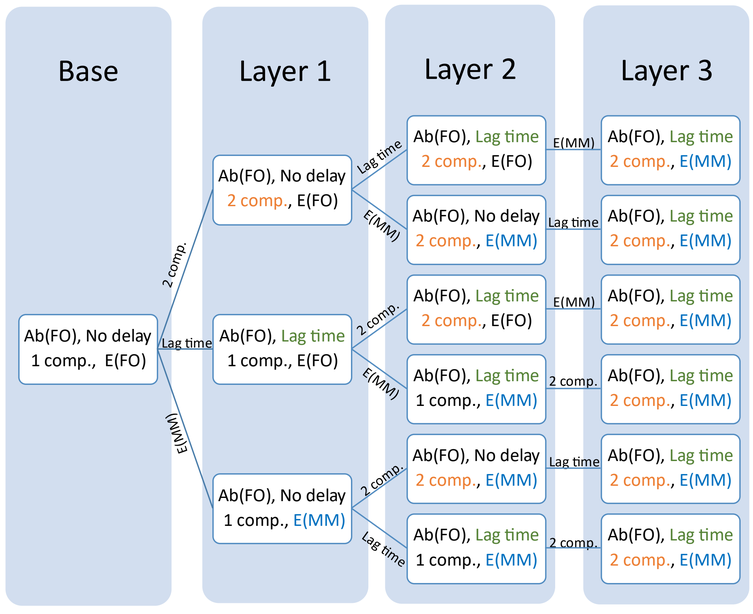

Figure 2. A representation for the model search workflow using the exhaustive stepwise algorithm. The search space contains 2 compartments model, lag time, and Michaelis-Menten elimination. Ab: absorption, E: elimination, FO: first-order, MM: Michaelis-Menten.

The **Modelsearch** tool was used to develop structural models for 10 clinical PK datasets (5 orally and 5 *i.v.* administered drugs).

A **starting model** for each dataset was generated using the **assemblerr** [3,4] package in R, which included:

- First-order (FO) absorption without any absorption delay (for oral drugs
- One-compartment disposition
- FO elimination
- A proportional residual error model.

The starting models were parameterized using clearance (CL), central volume of distribution (VC), and mean absorption time (MAT).

Model search approaches

In order to understand the influence of different **inter-individual variability (IIV) structures** for the model parameters on the final selected structural models, 5 approaches were investigated:

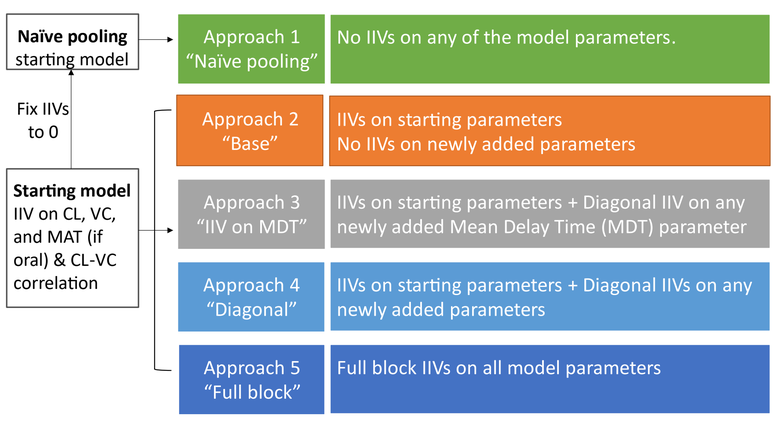

Figure 3. Model search approaches for structural model building

Table 1. The model search space included in the model search approaches evaluations.

Drug	Component	Included models
Oral	Absorption rate	FO, zero-order (ZO), and sequential ZO-FO
	Absorption delay	Lagtime, and 1, 3, and 10 transit compartments
	Distribution	One- and two- compartments
i.v.	Distribution	One-, two- and three- compartments
	Elimination	FO, Michaelis-Menten (MM), and mixed FO-MM

The **selection** of the final structural model was made based on the Bayesian Information Criterion (BIC) for mixed effects models which is described in equation (2.6) in reference [5].

Results

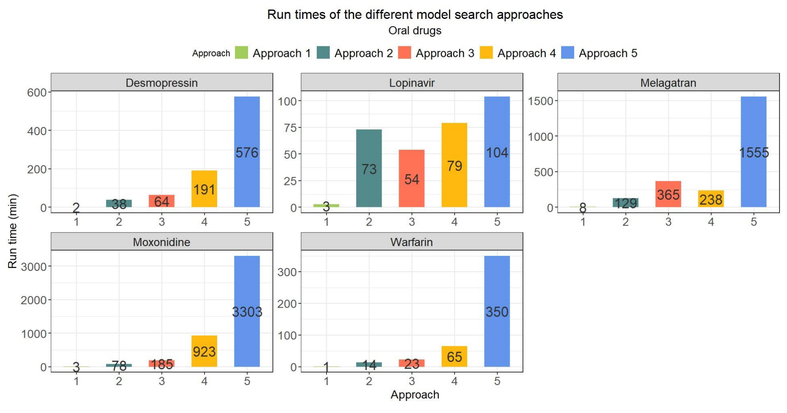

Figure 4. A comparison in model search run time for oral drugs across the different approaches. The time aspect in oral drugs is more crucial because of the large scope of search space.

Table 2. The selected structural models from the different model search approaches.

Dataset	Approach 1	Approach 2	Approach 3	Approach 4	Approach 5
	Naïve pooling	Base	IIV on MDT	Diagonal	Full block
Orally administered drugs					
Moxonidine	P1	P1-LAG	T10-P1	T10-P1	P1-T10
Warfarin	Ab(ZO)	P1-T3	T10	P1-T10[1]	P1-LAG-Ab(ZO)
Lopinavir	Ab(ZO)	Start model	Start model	Start model	Start model
Melagatran	Ab(ZO)-LAG	T3	T10	T10	T10
Desmopressin	T1-P1	Ab(ZO)-LAG	Ab(SEQ)-P1	Ab(SEQ)-P1	Ab(SEQ)-P1
i.v. administered drugs					
Gentamicin	P1	P1[1]	Not applicable	P1	P1[1]
Factor VIII	P1	P2		P2[1]	P1
Daunorubicin	P1	P1		P2[1]	P1
Pefloxacin	Start model	P1		P1	P1[1]
Tobramycin	P1	P1		P1	P1[2]

The models are named based on the changed or added features in comparison with the starting model. Ab: absorption, E: elimination, LAG: lag time, P1: 2-compartments, P2: 3-compartments, T_n: transit model with n compartments, ZO: zero-order.

[1] Minimization terminated due to rounding errors. [2] Minimization terminated due to hessian error (non-positive definite).

Conclusions

- The Modelsearch tool is able to automatically select a structural model with different strategies of setting the IIV model structure.
  - ✓ The same structural final model was selected in 7/10 cases across approaches 3-5.
  - ✓ Approach 5 had at least 3-folds slower run time in 4/5 oral drugs comparing to other approaches.
- The selected models with the default Modelsearch approach (Approach 3) gave the same, more complex (2-comp. instead of 1-comp.) or different (transit compartment instead of lagtime) structure than the published model. When the selected model was different, it was associated with an improvement in BIC compared to the published model structure.
- This automatic procedure enables the evaluation of numerous combinations of model components.
- An improved search algorithm is available in the tool which reduces the number of estimated redundant models.
- The Modelsearch tool is flexible and can support multiple research investigations for how to best implement structural model selection in a fully automatic model development workflow.

In collaboration with:

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[1] Model Search — Pharmpy 0.56.1 documentation. Available from: https://pharmpy.github.io/latest/modelsearch.html

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