Development of a Tool for Fully Automatic Model Development (AMD)

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Xiaomei Chen[1], Alzahra Hamdan[1], Shijun Wang[1], Tianwu Yang[1], Rikard Nordgren[1], Stella Belin[1], Zhe Huang[1], Simon J. Carter[1], Simon Buatois[2], João A. Abrantes[2], Andrew C. Hooker[1], Mats O. Karlsson[1]

[1]Department of Pharmacy, Uppsala University
[2]*Roche Pharma Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland*
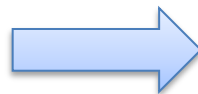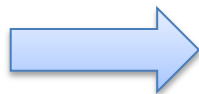
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Building a population PK model: iterative manual model fitting

model structure
random effects
RUV model
covariate model
outlier/influential individual

…

Final model

Time

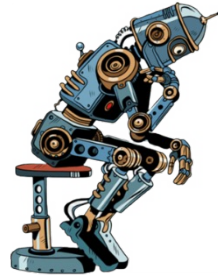Time

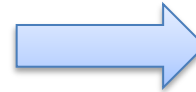# Building a population PK model: Automatic Model Development (AMD)

model scope
search algorithm
selection criterion
error handling
results output

…

Dataset

Final model

The **full** AMD tool is based on newly developed methods and our previous tools/methods

assemblerr	automatically generate model code for NONMEM
scm	stepwise covariate model building
resmod	screen extended RUV models by modeling CWRES data
new methods	newly developed methods for AMD

Pharmpy/pharmr

AMD
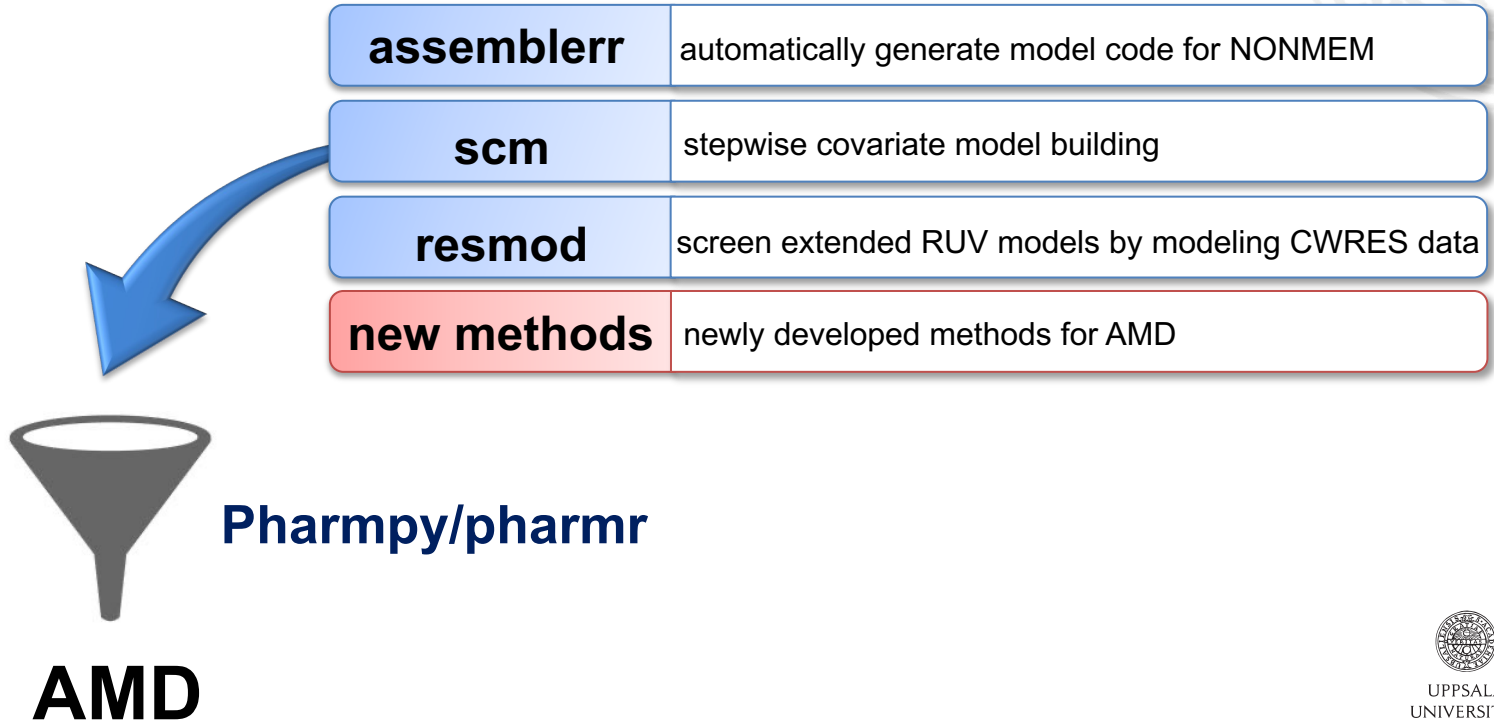
Workflow of the full AMD tool

IIV: inter-individual variation; **IOV**: inter-occasion variation; **cov**: covariates
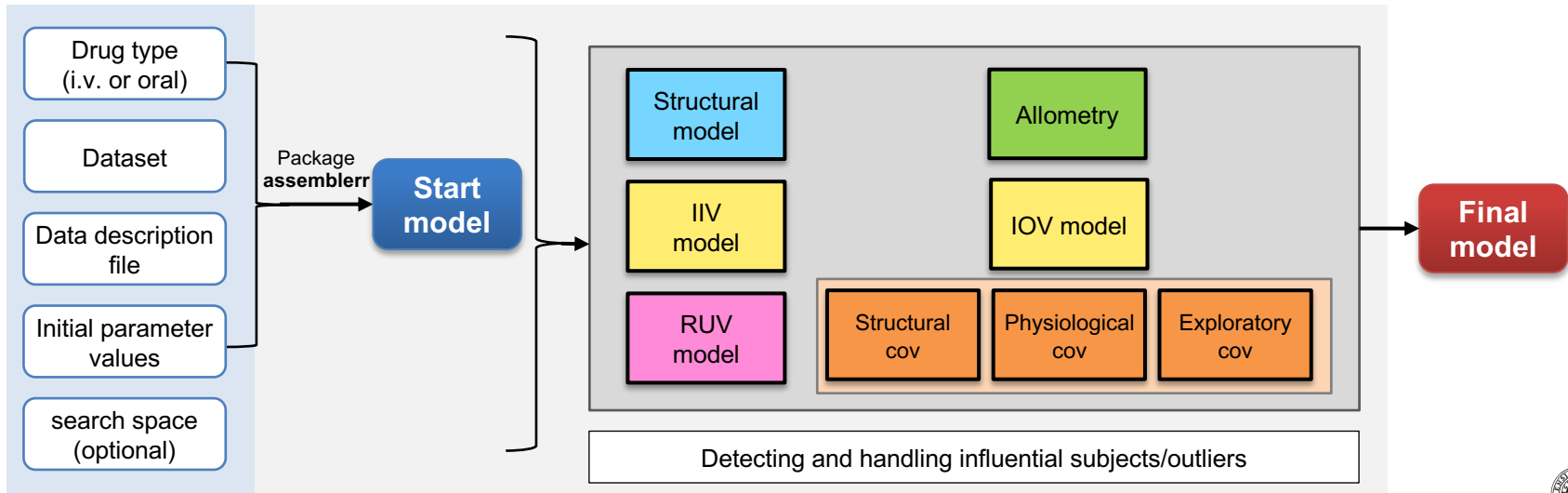
AMD modules in Pharmpy/pharmr can be used in the AMD workflow or separately
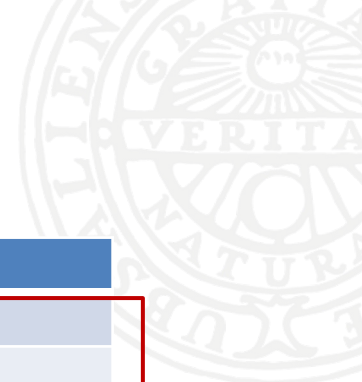
Module	Search Algorithm	Selection criterion
Structural model*	Exhaustive stepwise	BIC[1]
IIV model	2-step exhaustive • number of etas • omega matrix structure	BIC[2]
RUV model	3-stepwise resmod[3] • combined model, power model, IIV on RUV, time varying model	Likelihood Ratio Test (LRT)
Covariate model	Stepwise covariate model (SCM)	LRT
Allometry	User defined allometric model	-
IOV model	2-step exhaustive	BIC[2]
Detecting influential subjects/outliers	Prediction based on artificial neural network	

*For a small molecule PK after oral or i.v. administration

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1. Delattre M, Lavielle M, Poursat MA. J Stat. 2014;8:456–75.   2. Delattre M, Poursat MA. Int J Biostat 2016;16:75–83.
3. Ibrahim MMA, Nordgren R, Kjellsson MC, Karlsson MO. AAPS J.; 2018;20:1–9.

Structural model selection
Search algorithm: exhaustive stepwise

Start model

Absorption	Absorption delay	Distribution	Elimination
• FO • ZO • Sequential ZO and FO	• no delay • lag time • Transit comp models (n) with depot • Modified transit comp models (n) w/o depot	• 1-comp • 2-comp • 3-comp	• FO • ZO • Michaelis-Menten • FO with MM
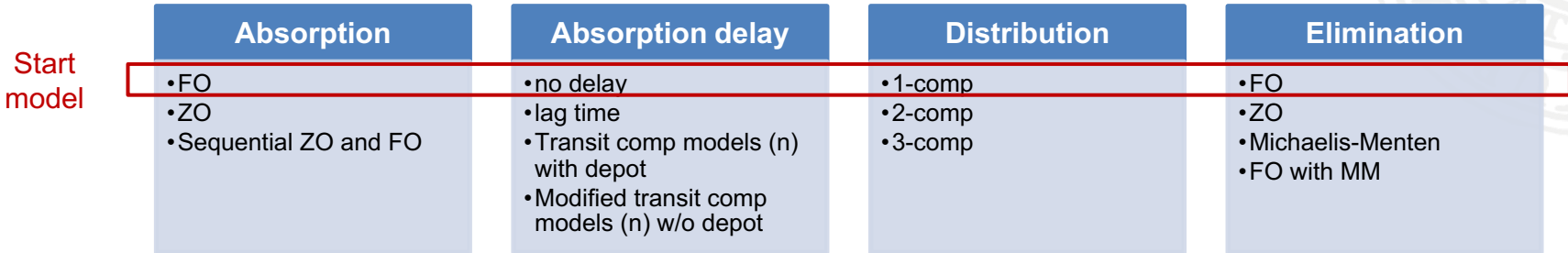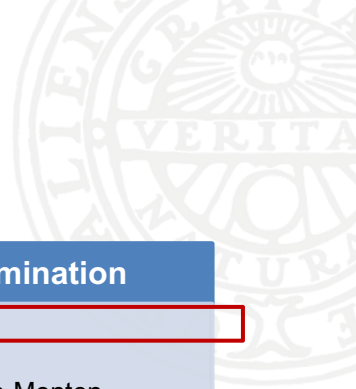
An example with reduced search space

Start model
Absorption: **first order**
Absorption delay: **no delay**
Distribution: **1-comp**
Elimination: **first order**

P1 17 — P1-T1 59
P1-T3 75
P1-LAG 106
T1 17 — T1-P1 59
T3 32 — T3-P1 75
LAG 92 — LAG-P1 91

drop of BIC from start model

worst model → best model
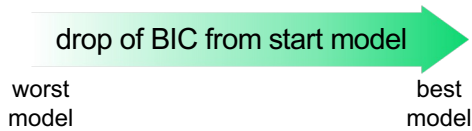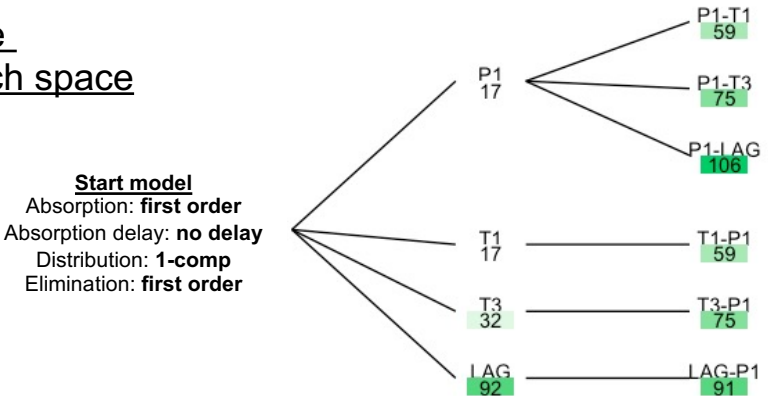
P1: 2-comp model
Tn: n-transit comp model
LAG: lag time

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IIV model selection
Search algorithm: 2-step exhaustive

input model → **search over ETA number** / Exhaustive algorithm → **search over IIV structure** / Exhaustive algorithm

```
              51    [CL,QP1,VC,VP1]
              35    [CL,VC,VP1]                    3    [CL,QP1,VC]+[VP1]
               0    [VC,CL]                        -9    [CL,VC,VP1]+[QP1]
              -5    [QP1,VC,VP1]                   -10    [QP1,VP1]+[VC,CL]
             -16    [CL,QP1,VC]                    -11    [QP1,VP1]+[VC]+[CL]
            -153    [CL,QP1,VP1]                   -12    [QP1]+[VP1]+[VC,CL]
            -296    [VC,VP1]                       -14    [QP1,VC,VP1]+[CL]
   0  [VC,CL]  -307    [CL,QP1]                    -21    [CL,QP1]+[VC,VP1]
            -312    [CL,VP1]                       -22    [CL,QP1,VP1]+[VC]
            -339    [QP1,VP1]                       -22    [CL,QP1]+[VC]+[VP1]
            -348    [CL]                           -23    [CL]+[QP1]+[VC,VP1]
            -360    [QP1]                          -25    [CL,VP1]+[VC,QP1]
            -468    [VP1]                          -26    [CL,VP1]+[VC]+[QP1]
            -694    [VC,QP1]                       -27    [CL]+[VP1]+[VC,QP1]
            -727    [VC]                           -35    [CL]+[QP1]+[VC]+[VP1]
            -827    No_iiv
```
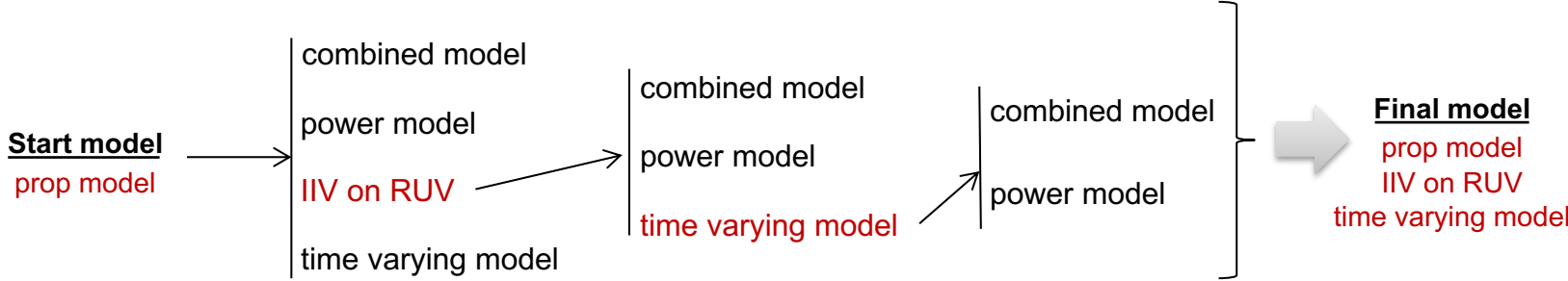
selected model in each step based on BIC

[X,Y]:   covariance between X and Y

[X]+[Y]:   diagonal omega structure
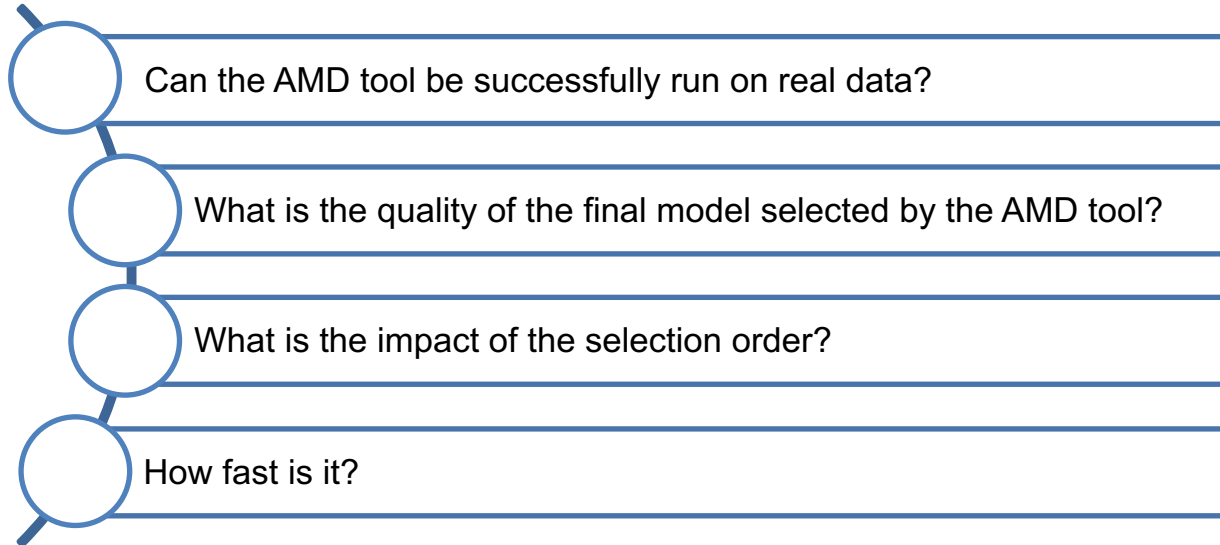
The drop of BIC from last step

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RUV model selection:
Search algorithm: 3-stepwise resmod

selected model in each step based on p-value of LRT

Ibrahim MMA, Nordgren R, Kjellsson MC, Karlsson MO. Variability Attribution for Automated Model Building. AAPS J 2019 ;21:1–8.

The questions we want to answer through the initial evaluation

Can the AMD tool be successfully run on real data?

What is the quality of the final model selected by the AMD tool?

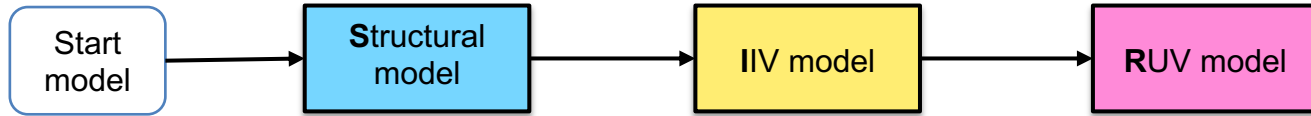What is the impact of the selection order?

How fast is it?

The AMD tool evaluation on 10 datasets

Drug	Administration	Number of subjects	Number of observations
gentamicin	*i.v.*	210	574
daunorubicin	*i.v.*	41	112
factorVIII	*i.v.*	34	714
pefloxacin	*i.v.*	74	337
tobramycin	*i.v.*	155	388
desmopressin	oral	28	373
lopinavir	oral	30	315
melagatran	oral	167	1177
moxonidine	oral	73	1006
warfarin	oral	32	246

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3 orders of model selection were tested for the impact of the order

SIR
Start model → **S**tructural model → **I**IV model → **R**UV model

RSI
Start model → **R**UV model → **S**tructural model → **I**IV model

SRI
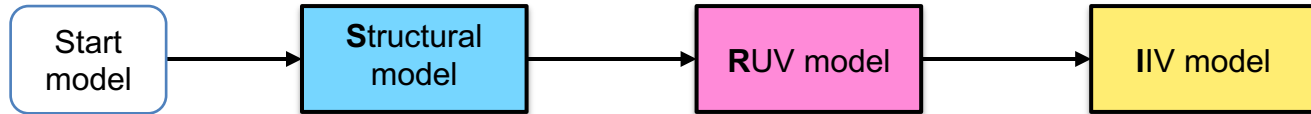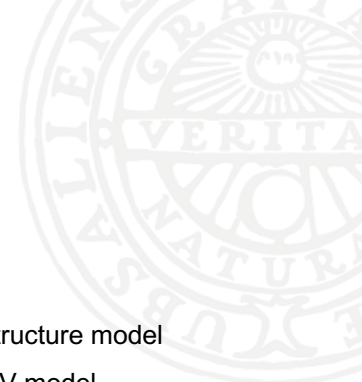Start model → **S**tructural model → **R**UV model → **I**IV model
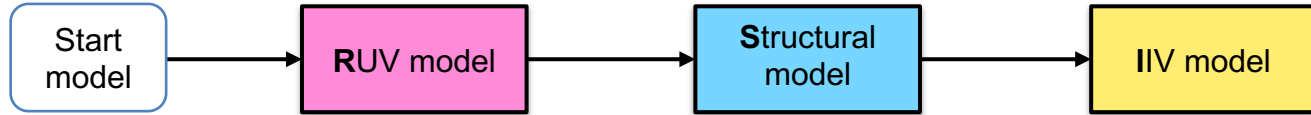
S: Structural model
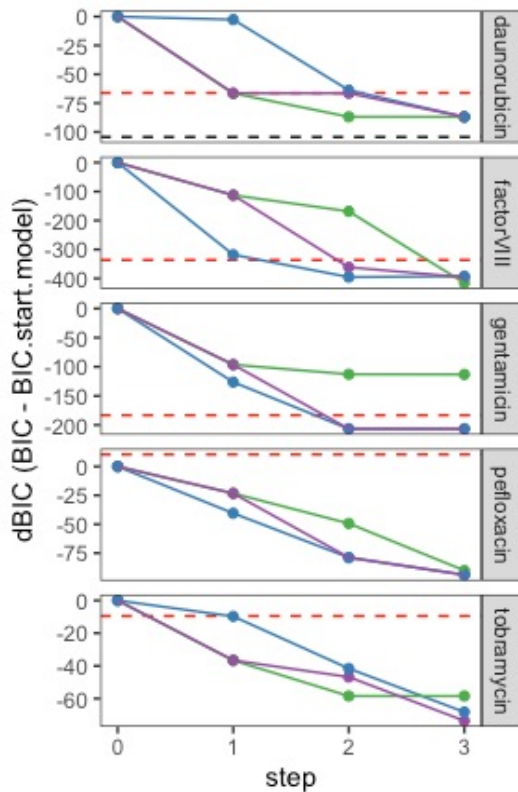I: IIV model
R: RUV model

Start model
- structural model: 1-comp model with 1st-order elimination (and 1st-order absorption)
- IIV model: [CL, V] or [CL,V]+[MAT]
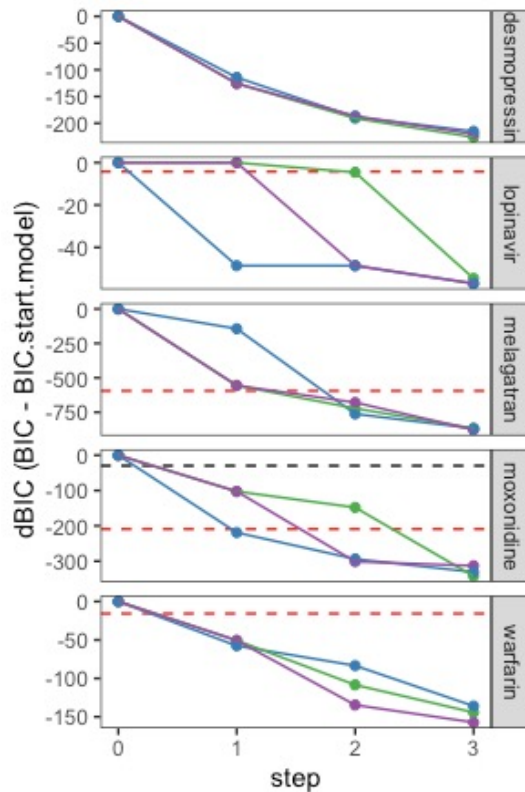- RUV model: proportional model

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The 3 orders gave similar BIC

i.v. drugs

oral drugs

RSI   S: structure model

SIR   I: IIV model

SRI   R: RUV model

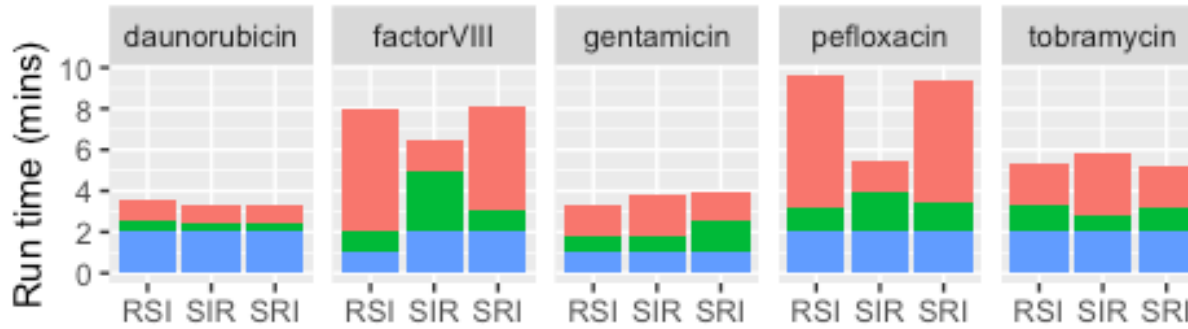— — *Published model on normal scale data

— — +Published model on log scale data

*The modified published models with only model structure, IIV, and RUV

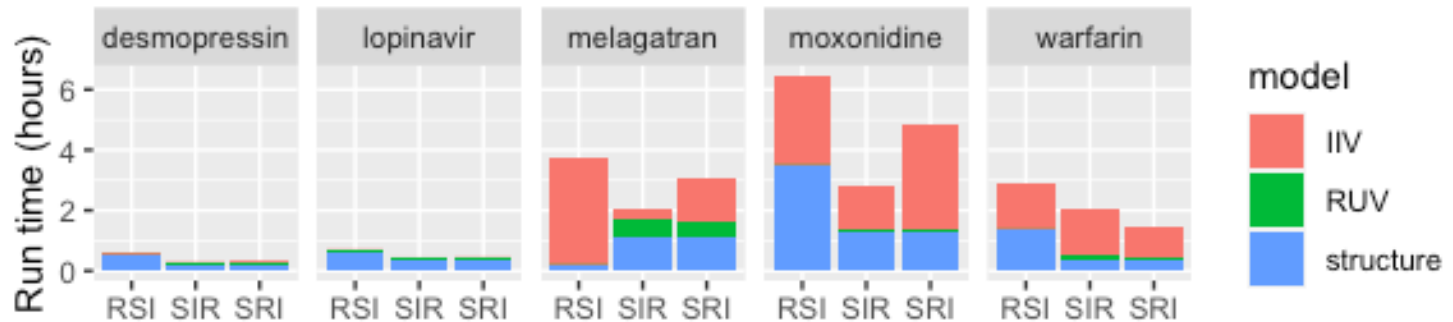+Some published models were originally fitted to log-transformed data

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The AMD running time:
i.v. drugs 3-10 min; oral drugs: 17 min-6.5 hours

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Summary of the initial evaluation

| Can the AMD tool be successfully run on real data? | ➡ | Yes. on all the 10 datasets |

| What is the quality of the final model selected by the AMD tool? | ➡ | Good, by comparison to the published models |

| What is the impact of the selection order? | ➡ | o The 3 orders gave similar BIC
o No order gave the lowest BIC for all the 10 datasets |

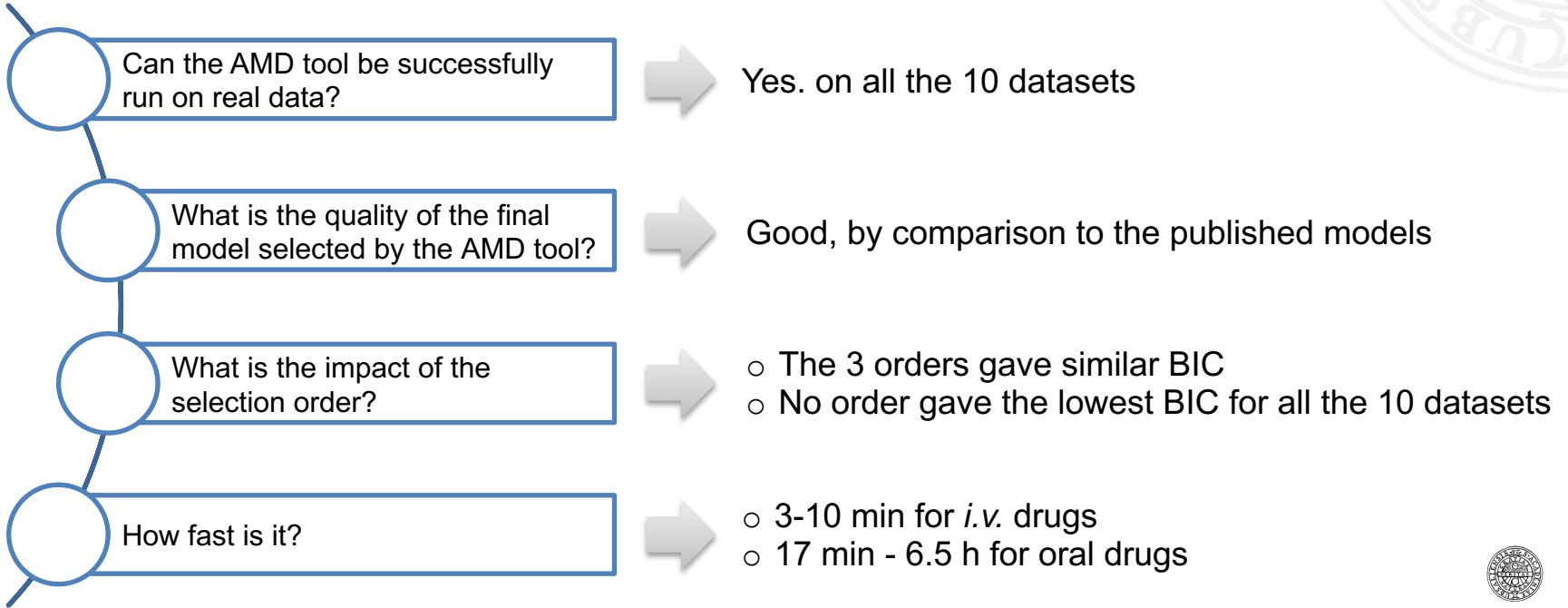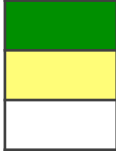| How fast is it? | ➡ | o 3-10 min for *i.v.* drugs
o 17 min - 6.5 h for oral drugs |

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Properties of the AMD tool

- Systematic, extensive, objective, flexible, model building

- Requires a good knowledge of relevant model scope

- Allows evaluation and improvement of standard model building practices

- Avoids human coding errors

- Sensitive to software bugs

- Frees modeler's time for other tasks

Development status

	Done
	Ongoing
	To do/Under consideration

Module	Implemented	Initial testing on 10 datasets	Method improvement
Structural model			Additional modules (PKPD etc.)
RUV model			Automatic selection of normal vs log-scale
IIV model			More efficient search algorithm and method; Semi-parametric distributions
IOV model			
Allometry			
Covariate model			More efficient search algorithms and method
Influential subjects/outliers			Allow AMD actions based on such results
AMD workflow with all the modules			Allow more selection criteria; Extensive testing;

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Welcome to our AMD posters

- **S-07   Entire meeting**   Rikard Nordgren:
  - Pharmpy: a versatile open-source library for pharmacometrics

- **IV-30   Thursday 15:00**   Alzahra Hamdan
  - Automatic Development of Pharmacokinetic Structural Models – Pharmpy Model Search Tool

- **IV-11   Thursday 15:00**   Simon Carter
  - The development of artificial neural networks for the prediction of influential individuals and outlying individuals and their application during the model building process

- **IV-31   Thursday 15:00**   Zhe Huang
  - Comparison of PK models using normal and log-transformed scale data

- **I-01   Wednesday 9:45**   João A. Abrantes
  - ADaMO: End-to-end automation of Pharmacometric modelling in drug development, from dataset building to output generation

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If you want to use our AMD and other Pharmpy tools

- Pharm**py**/pharm**r** is available in Python and R

- Download the most recent version:
  https://github.com/pharmpy

- Pharmpy manual:
  https://pharmpy.github.io

Acknowledgement
for tool testing and feedback

Roche

Emilie Schindler

Franziska Schädeli Stark

Nicolas Frey

Sylvie Retout

Valérie Cosson

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Thank you for listening!

Questions?