qPnoMAD: A Residual-Trend-Based, ML-Guided Tool for Automated PopPK Model Development

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qP's nonlinear mixed-effects Model Automated Developer

- PopPK model development is traditionally iterative and subjective, but based on quantifiable heuristics
- Machine learning can be used to automate decision-making in model building
- Trends in residuals can point towards plausible next modelling steps
- **qPnoMAD** automates structural and stochastic popPK model development

Overall model building strategy

1. **Initialize** with simple model: first-order elimination, IIV on CL
2. **Select next component** using Random Forest (RF) classifier
3. **Estimate new model** using NONMEM
4. **Evaluate improvement** based on statistically significant ΔOFV
5. **Repeat** from step 2 until no further significant improvements

Random Forest Classifier guides next component proposal based on features

Inputs:

- Training data (features from simulated data with known true model)
- State (current model structure)
- Possible next states (candidate component, e.g. 2nd CMT or IIV)
- Test data (features of current model)

Process:

For each candidate component per modelling step:

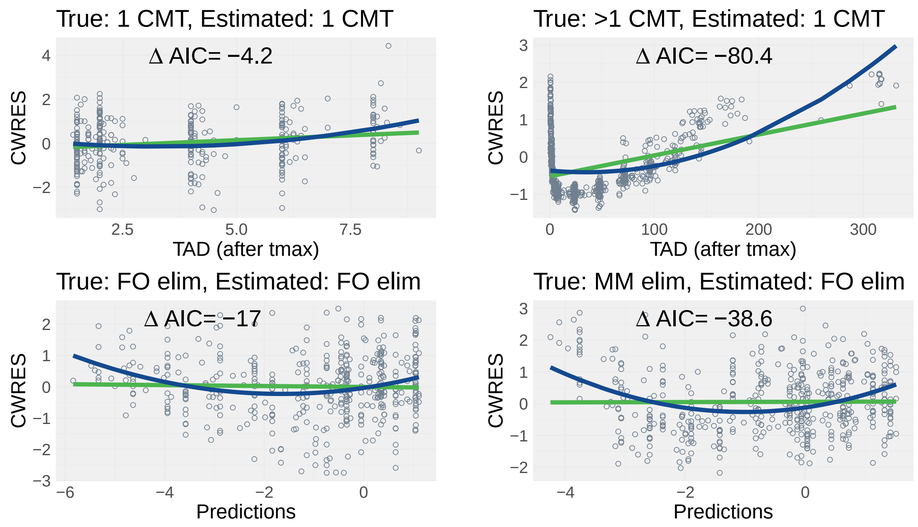
1. **Filter training data**: retain rows with structurally compatible components to the current estimated state (e.g., same elimination structure when testing elimination)
2. **Train a Random Forest** (1000 trees, max depth 10, fixed seed) using selected features
3. **Predict probability** for each component

Output:

- Proposed component to turn on/off next

Features used for the classifier:

- AIC difference between a linear and a quadratic relationship between:
  - CWRES vs. TAD prior to t_{max}
  - CWRES vs. TAD after t_{max}
  - CWRES vs. PRED
- The sign of the second-order parameter (positive: ∪ , negative: ∩)
- For each IIV parameter: the p-value of a test of variance homogeneity (Fligner-Killeen) between the post-hoc ETAs and a reference distribution with 15% CV



Example Feature means for filtered estimated and varying true models:

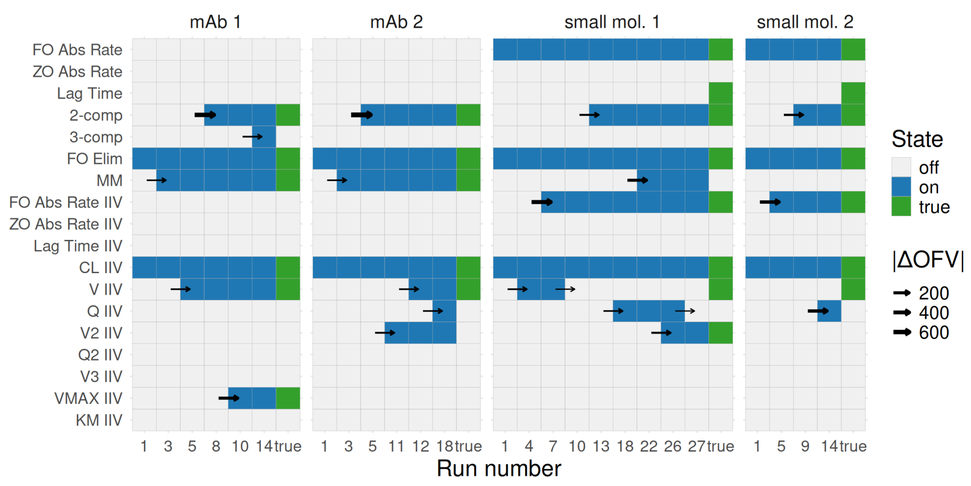
	True Elimination		True Compartments	
Feature	FO	MM	1	>1
$\Delta AIC_{TAD<tmax}$	-19	-2.4	-13	-24
$\Delta AIC_{TAD>tmax}$	-28	-39	-4.2	-82
ΔAIC_{PRED}	-17	-39	-8.1	-44
$sign_{TAD<tmax}$	-0.063	-0.11	-0.049	-0.11
$sign_{TAD>tmax}$	0.53	0.52	0.44	0.72
$sign_{PRED}$	0.32	0.42	0.26	0.48

Estimated model: 1 compartment with FO elimination. True models: FO or MM elimination and 1 or 2-3 compartments. Feature means differ by true model, indicating discriminative value.

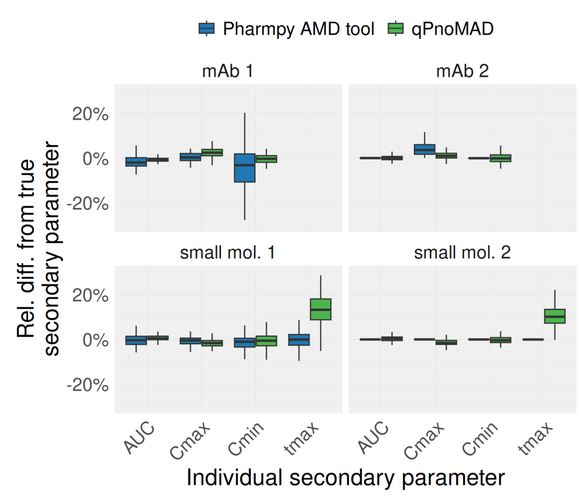
Evaluation on simulated data

- Simulated (modified) base models from published drug development programs
  - Small molecule [1]
  - mAb [2]
- Simulated study designs (Phase I and II, SAD/MAD) align with true model studies
  - Small molecule: 143 IDs, 18-29 samples per ID
  - mAb: 100 IDs, 13-31 samples per ID
- qPnoMAD and Pharmpy AMD tool 1.6.0 [3] performance evaluated on all datasets

Results: Modelling process



Results: Secondary PK



Challenges → Future work

Choice of Initial values	→ multiple start values/option to manually change initial values during the process
Unstable runs (adding IIV may lead to higher OFV)	→ check condition number and successful minimisation
Repeated checks of the same components	→ add penalty for recently checked components
Michaelis-Menten is slow and often evaluated early on	→ downweigh Michaelis-Menten component
True model is not necessarily best (in terms of OFV)	→ investigate overfitting and evaluation approaches

Conclusion: qPnoMAD can guide popPK model selection

- Parsing less models than an exhaustive search we arrive at a fit-for-purpose model
  - qPnoMAD tested between 20 and 35 models in total
  - In comparison, Pharmpy often tests more than 100 models
- While the true models were not identified in the test cases, the secondary PK parameters were accurate
- Model building approach mimics a trained pharmacometrician's process and can be interpreted similarly
- ! Opportunity to speed up initial model development considerably to focus on manual refinement and further modelling

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References:

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[3] Chen X, et al. A fully automatic tool for development of population pharmacokinetic models. *CPT Pharmacometrics Syst Pharmacol*. 13: 1784-1797. (2024)