

Multi-Objective Optimization for Population Pharmacokinetic Model Selection: Evaluating NSGA-III Performance



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Introduction

- In pharmacometric model selection, there is typically a trade-off between model fit and parsimony. In addition, the model fit metrics (e.g. -2ll) may be insensitive to clinically relevant parameters, such as C_{max} or C_{min}.
- Commonly, the selection of the “best” model among competing objectives is subjective, given these trade-offs.
- Non-dominated sorting genetic algorithm III (NSGA-III) is an evolutionary algorithm intended to solve multi-objective optimization (MOO) problems, particularly those with 3 or more objectives, by applying a reference point based non-dominated sorting approach [1].

Aims

This study aims to evaluate the performance of NSGA-III in the context of PopPK model selection, assessing its ability to optimize multiple competing objectives.

Methods

- Emtricitabine (FTC) and emtricitabine triphosphate (FTC-TP) PK data from the CONRAD 137 study [2] were used in this analysis. 2114 observed concentrations (1126 plasma FTC concentrations and 988 PBMC FTC-TP concentrations) from 120 female subjects were included. PK data from the single dose phase and multiple dose phase were merged. In this analysis, the search space was defined as follows.
 - Number of compartments for plasma FTC (1|2|3)
 - With or without an absorption lag time
 - The formation kinetics of PBMC FTC-TP from plasma FTC (Linear|Michaelis-Menten)
 - The elimination kinetics of PBMC FTC-TP (Linear|Michaelis-Menten)
 - With or without between subject variability on V₂, Q₂, V₃, and Q₃
 - Residual error model of plasma FTC (additive|proportional|combined additive and proportional)
 - Residual error model of PBMC FTC-TP (additive|proportional|combined additive and proportional)
- MOO was implemented as a new search method in pyDarwin [3]
- NSGA3 algorithm was used to conduct multi-objective optimization with 3 optimization criteria:
 - Objective function values (-2LL, OFV)
 - Number of total estimated parameters
 - Bias in steady-state PBMC FTC-TP trough concentration prediction
- The OFV measured goodness-of-fit, ensuring the model adequately describes the dataset.
- The number of estimated parameters (THETA, OMEGA and SIGMA) served as a parsimony criterion for model simplicity.
- The prediction bias in steady-state PBMC FTC-TP concentration ensured the model captured clinically relevant exposure.
- Inequality constraints removed crashed NONMEM runs. We ran NSGA-III with 12 partitions for 15 generations, using a population size of 92 in each generation.
- The final Pareto front from NSGA-III was compared with the model developed using the traditional stepwise method.

Results

Traditional Model Selection Method

- The traditional stepwise method final model has 3 compartments for plasma FTC, with saturable formation kinetics of PBMC FTC-TP using Michaelis-Menten equation and a linear elimination from PBMC.
- The OFV of the final traditional selection model is 3543.015, with 18 parameters estimated.
- There is a 9.03% bias in steady-state PBMC FTC-TP trough concentration prediction.

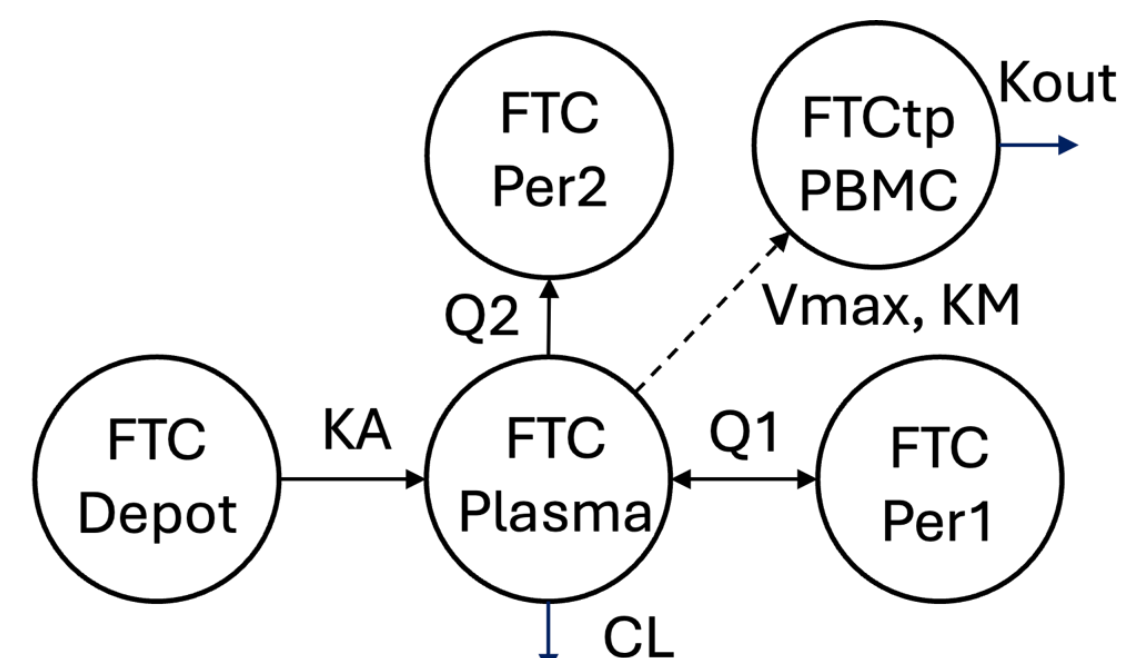


Figure 1: Final model structure selected by traditional model selection method

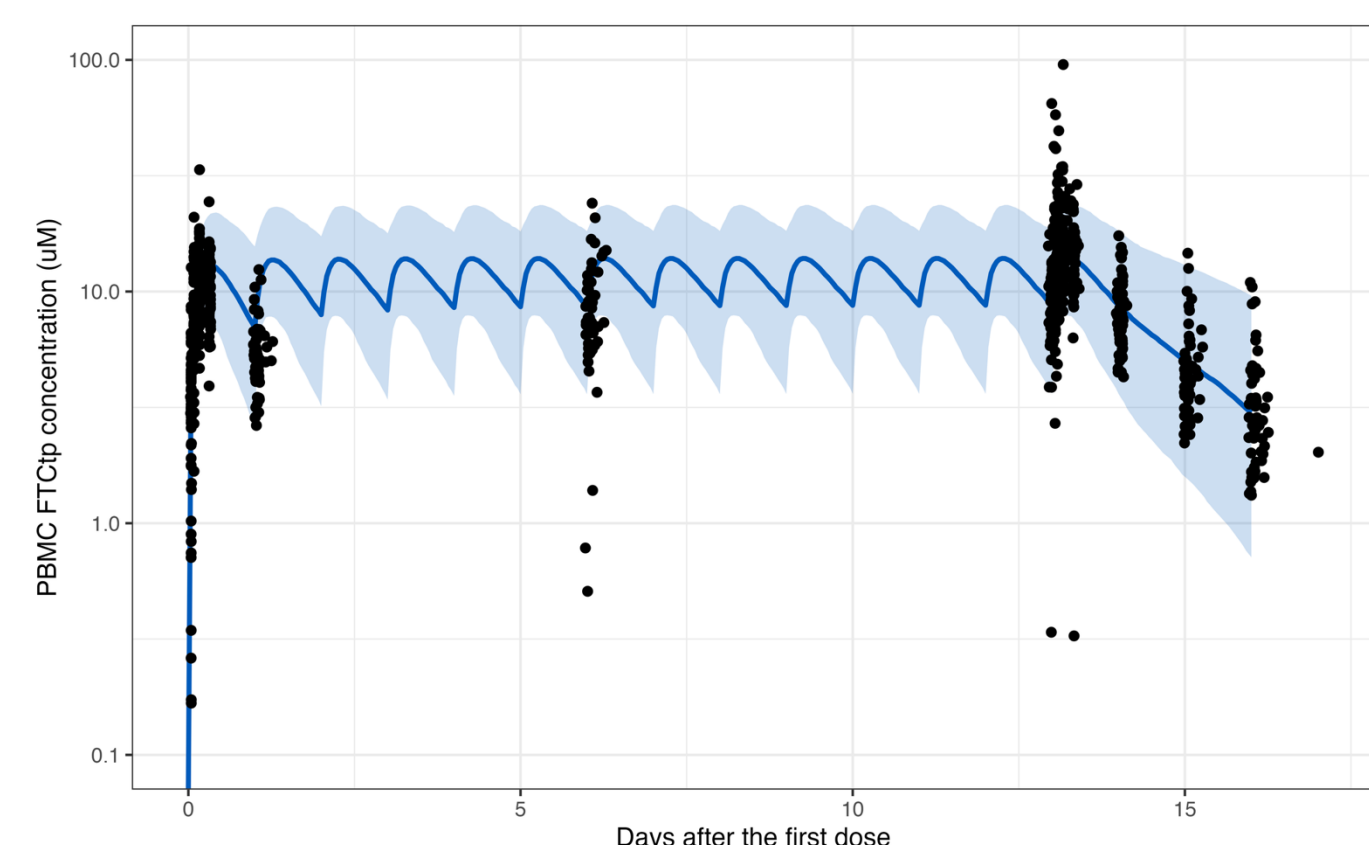


Figure 2: Concentration-time profile for PBMC FTC-TP. Simulation for 14 days oral 200 mg FTC every 24 hours in 1000 virtual patients

Results

NSGA-III Model Selection

- The NSGA-III algorithm identified a Pareto front consisting of 30 models from the search space, with the OFV ranging from 3520.126 to 10134.822 and the total number of estimated parameters varying between 12 and 24.
- Among the identified Pareto fronts, the bias in steady-state PBMC FTC-TP trough concentration ranged from 0.24% to 98.09%.
- This Pareto front illustrates a trade-off between model complexity and predictive performance.

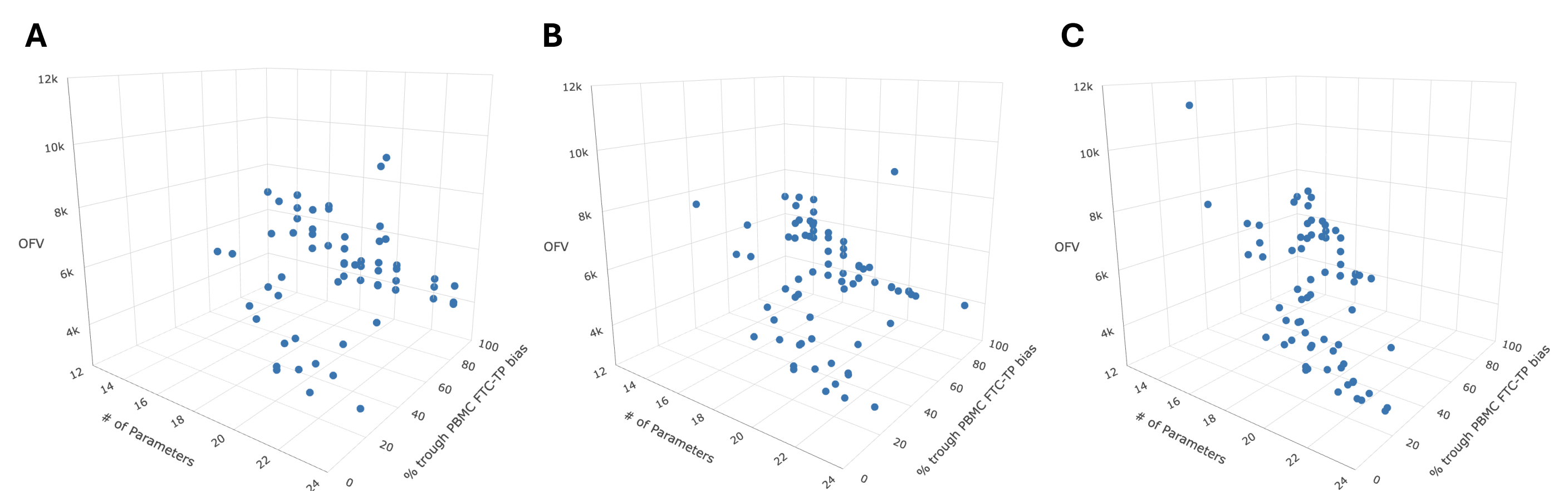


Figure 3: Parents of the first 3 generations (A-C) selected by NSGA-III. Each panel shows the non-dominated solutions from the corresponding generation in the objective space. The plots illustrate how the selected solutions progressively move toward the Pareto front while maintaining diversity

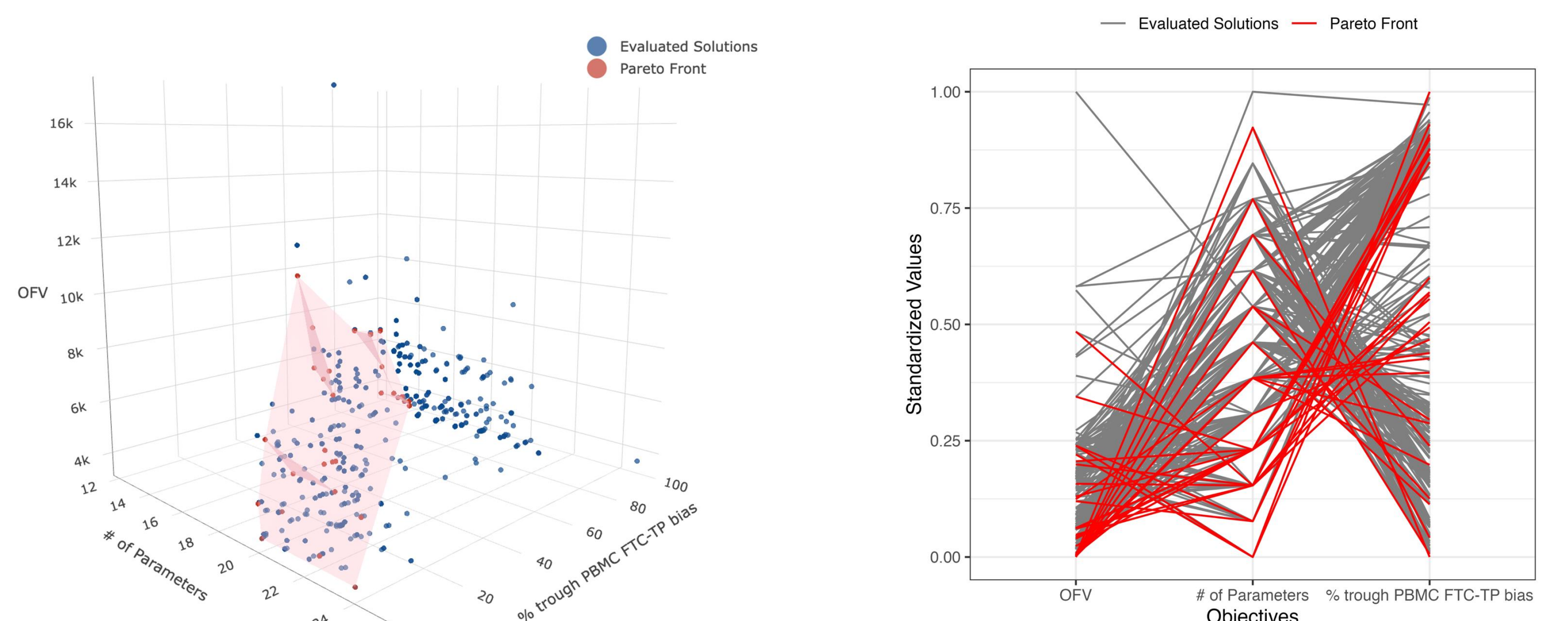


Figure 4: Final Pareto front selected by NSGA-III

Figure 5: Trade-off between model complexity and predictive performance

Table 1: Results of the optimization criteria for traditional model selection and the set of non-dominated models from the NSGA-III search

Algorithm	OFV range	Number of estimated parameters range	% trough PBMC FTC-TP concentration bias range
NSGA-III	3520.126 - 10134.822	12 - 24	0.24%-98.09%
Traditional model selection method	3543.015	18	9.03%
MOO model with similar parsimony to Traditional	3546.311	18	11.32%

Conclusion

- We successfully implement NSGA-III in pyDarwin, enabling MOO with reference point based non-dominated sorting.
- The Pareto front identified by NSGA-III provides a broader view of the optimal solution space and offers insights into the trade-offs between the competing objectives.
- The NSGA-III algorithm with one of the optimization criteria as bias in PBMC FTC-TP concentration was able to identify a set of models in which some of the models had less bias than traditional methods.
- The selection of the final model(s) from among these non-dominated models is left to the pharmacometrician as a subjective decision based on the objectives of the analysis, biological plausibility, and examination of diagnostic graphics.

References

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- [2] Thurman AR, Schwartz JL, Cottrell ML, Brache V, Chen BA, Cochón L, Ju S, McGowan I, Rooney JF, McCallister S, Doncel GF. Safety and Pharmacokinetics of a Tenofovir Alafenamide Fumarate-Emtricitabine based Oral Antiretroviral Regimen for Prevention of HIV Acquisition in Women: A Randomized Controlled Trial. EClinicalMedicine. 2021 May 23;36:100893.
- [3] <https://certara.github.io/pyDarwin/html/index.html> Accessed 22 May 2025