ADaMO: End-to-end automation of Pharmacometric modelling in drug development, from dataset building to output generation

João A. Abrantes, Kevin Smart, Claire Petry, Félix Jaminion, Guillaume Schmitt, Nicolas Frey, Clarisse Chavanne, Simon Buatois

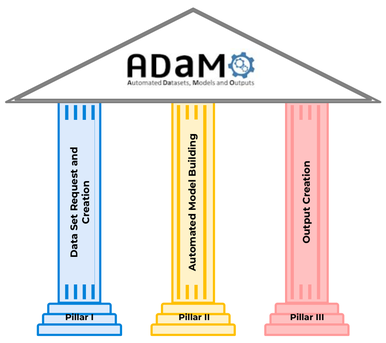
Roche Pharma Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland

Background

- The **A**utomated **Da**tasets, **M**odels and **O**utputs (**ADaMO**) initiative seeks to automate and streamline pharmacometric processes used for informing decision-making in drug development
- The manual creation of datasets for modelling, development of population models and respective reports are complex, arduous and time-consuming processes
  - the time spent in these activities tends to be longer than the time invested in using the models to inform the clinical development of compounds

The 3 pillars of ADaMO

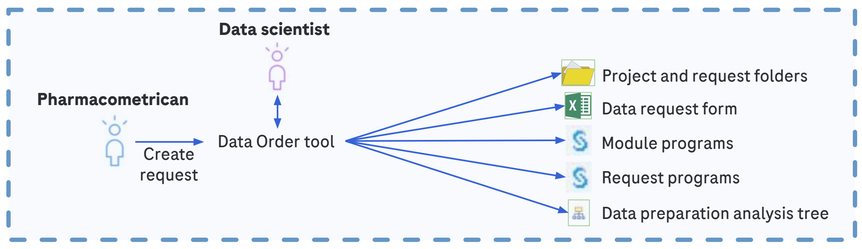
- The ADaMO initiative has been developed in a validated computational environment [1, 2], Scinteco improve, where data, models and outputs are generated and stored
- ADaMO consists of three pillars that cover the end-to-end Pharmacometric modelling process
  - **pillar I**: automated dataset request and creation
  - **pillar II**: automated model building
  - **pillar III**: automated output creation



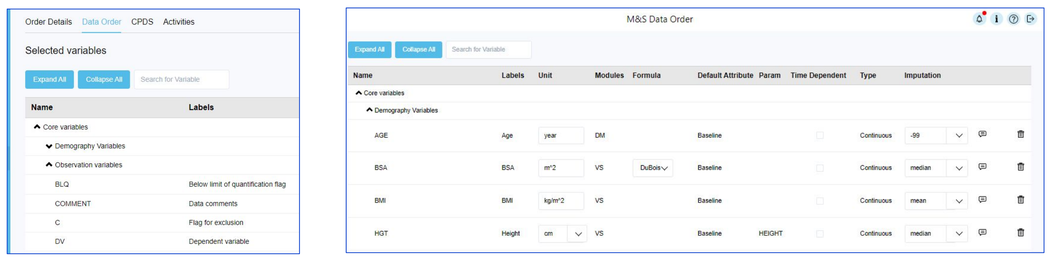
Pillar I : A dataset for population modelling is produced using scripts generated automatically

The process starts with the user completing a data request form in a user-friendly web app, indicating the variables to be included in the dataset (e.g. demographic variables, subjects and dependent variable with definition of units, formulas and imputation rules). After reviewing the request, a data scientist triggers the automatic generation of SAS scripts in a validated GCP compliant environment where data is generated and stored [1,2]. Finally, the dataset undergoes QC and the user is automatically notified that the dataset has been created. In this pillar, automation simplifies and speeds-up the process of dataset request and creation, providing increased robustness as the scripts generated are reusable.

Representation of the general workflow of pillar I



Screenshots of the interface of the data order tool



Pillar II: A PK model is developed automatically using NONMEM

A heuristic algorithm is being developed to create a population PK model and optimise its components (e.g. structural, inter-individual variability, residual error models) automatically with the goal of reaching a final PK model developed in NONMEM [3]. For this purpose, an initial NONMEM model is generated from scratch using the open-source R package assemblerr (https://uupharmacometrics.github.io/assemblerr) [4], and its parameters are estimated using NONMEM directly in R using PharmR, an R wrapper for Pharmpy (https://pharmpy.github.io) [5]. Thereafter, the automatic process continues with the model being modified (e.g. structural model challenged) and a series of candidate models being generated. These are tested and the best model is selected based on pre-specified statistical criteria. In this pillar, automation speeds-up PK model development and it increases its robustness by using predefined algorithms.

Representation of the general workflow of pillar II

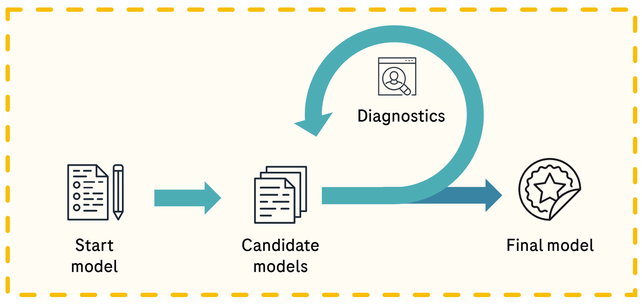
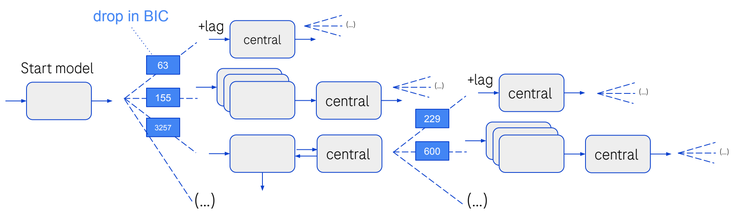
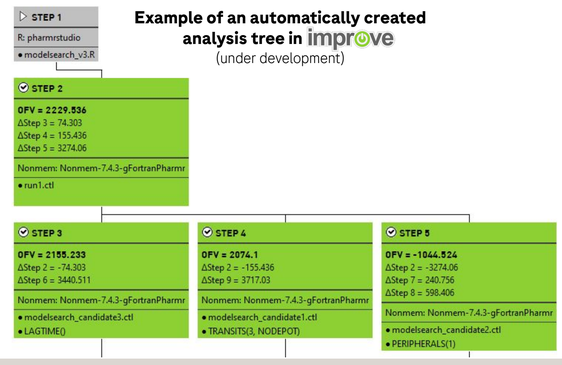


Illustration of an automatic structural model development workflow



For detailed information on model development algorithms, check the Pharmpy manual available at https://pharmpy.github.io

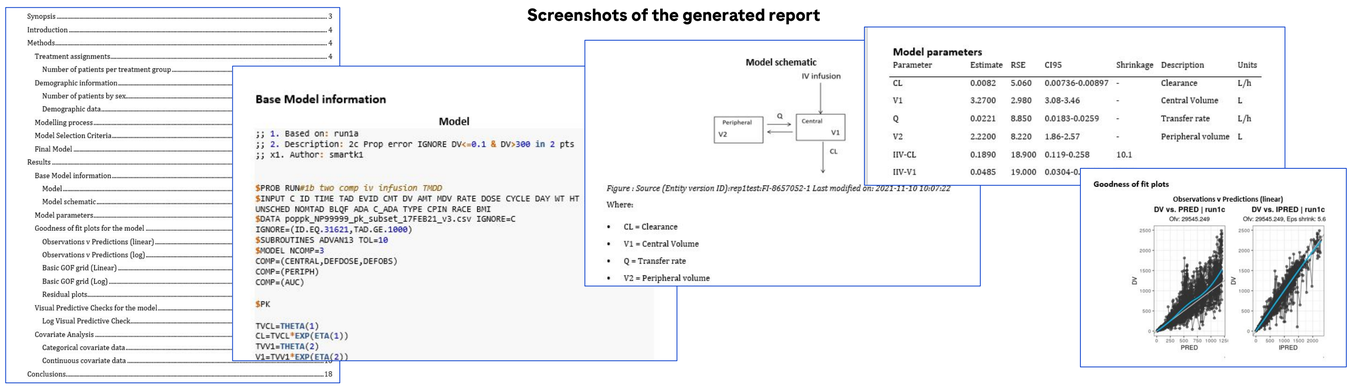
Example of an automatically created analysis tree in improve
(under development)



Pillar III: A modelling report is pre-populated automatically

A series of R markdown scripts and an R library have been created which allow direct incorporation of model outputs (e.g. GOF plots, parameter tables, VPC) into a word report. By automatically combining the structure of a report with model outputs (main tables and figures), the reporting process has been substantially speeded up resulting also in fewer typographical and carry over errors.

Screenshots of the generated report



Conclusion

- A solution to automate end-to-end Pharmacometric modelling has been developed
- The current scope of ADaMO includes classical PK models for a single entity in pillar II, and pillars I and III already go beyond this scope, supporting more advanced PK and PK/PD analyses
- While the full potential of the solution will only be achieved through the integration of all three pillars in one computational environment, it is possible to use each component on its own
- Automation boosts quality, reproducibility and frees time for pharmacometricians to use the model outcomes to influence clinical trials, address more complex modelling tasks and increase the number of supported projects

References

[1] Improve – Modeling and simulation platform. PAGE (2016). Abstr 6073.

[2] Usage of a validated environment to support modeling and simulation activities. Buchheit *et al.* ACoP11. 2020.

[3] Development of a tool for fully automatic model development (AMD). Chen *et al.* PAGE (2022). Abstr 10091.

[4] Pharmpy and assemblerr - Two novel tools to simplify the model building process in NONMEM. Nordgren *et al.* PAGE (2021). Abstr 9656.

[5] Pharmpy: a versatile open-source library for pharmacometrics. Nordgren *et al.* PAGE (2022). Abstr 10096.

Acknowledgements

This work was supported by F. Hoffmann-La Roche Ltd., Basel, Switzerland. The authors would like to acknowledge the contributions of the following individuals: Wolfgang Schwarzenbrunner and Christian Flandorfer from Scinteco (pillar I); Prof. Mats Karlsson, Prof. Andrew Hooker, Alzahra Hamdan, Aurelien Ooms, Osama Qutishat, Piyanan Assawasuwannakit, Rikard Nordgren, Sebastian Ueckert, Shijun Wang, Simon J. Carter, Stella Belin, Tianwu Yang, Xiaomei Chen and Zhe Huang from the Department of Pharmacy, Uppsala University, Sweden (pillar II), and; Michael Hackl from Scinteco (pillar III). In addition, the authors would like to thank Henry Hofmann for project management, and Emilie Schindler, Franziska Schaedeli Stark, Julie Cabanel, Sébastien Jolivet, Sylvie Retout, Valérie Cosson, and Vincent Buchheit for their assistance with testing.