

Enhancing population PK modeling efficiency using an integrated workflow

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Background

Population pharmacokinetic (popPK) modeling constitutes a substantial area of Pharmacometrics. PopPK activities need to be performed regularly during drug development - from first-in-human dose prediction to submission and beyond. Since such analyses currently can take a considerable amount of time, resources are bound and not readily available to support other aspects of model based drug development.

Some of the reasons for the long duration of popPK analyses lie in the lack of standards for

- Model building methodology adapted to the needs of the Pharma industry
- Data specifications allowing efficiency
- Computational tools/methods typically used.

Main drivers for model building decisions are

- Scientific reasons
- Data availability
- Issues deriving from a specific tool/approach.

Objectives

The aims of this work have been to examine how the process of popPK modeling can be supported in order to

- Increase efficiency
- Raise the level of trust in the final model(s)
- Industrialize the PK modeling approach.

To demonstrate the feasibility, a proof-of-concept popPK workflow tool was implemented.

Conclusion

The presented approach to popPK modeling consists of a standard workflow containing:

- 1) Standard dataset specification,
- 2) Graphical exploration,
- 3) Data cleaning,
- 4) Model building (structural and covariates).

Additional analyses, such as model comparison, sensitivity and robustness analyses are integral parts of this approach.

The approach has been tested internally on a number of projects and has shown to considerably improve efficiency and reliability.

The proof-of-concept of this workflow follows the Pareto principle. It covers the most common (>80%) of the popPK cases.

Methods

1. Definition of a standard dataset specification supporting popPK and popPKPD analyses
2. Analysis of the space of popPK models that covers >80% of cases in an industrial setting
3. Definition of a standard popPK workflow
4. Implementation of the standard workflow in SBPOP[1] as proof-of-concept
5. Test/validation of the workflow on a wide variety of popPK modeling activities
6. Training of associates with provided material

Results

1) Standard dataset specification

Analysis of past activities indicated that many different dataset specifications were used. This increased the likelihood of mistakes in the specifications and data preparation. This leads to time consuming iterations for dataset correction and validation.

We defined a standard dataset specification that is more exhaustive (and thus different in format) to that required by any NLME modeling software. However, it can be automatically converted into all tool specific formats.

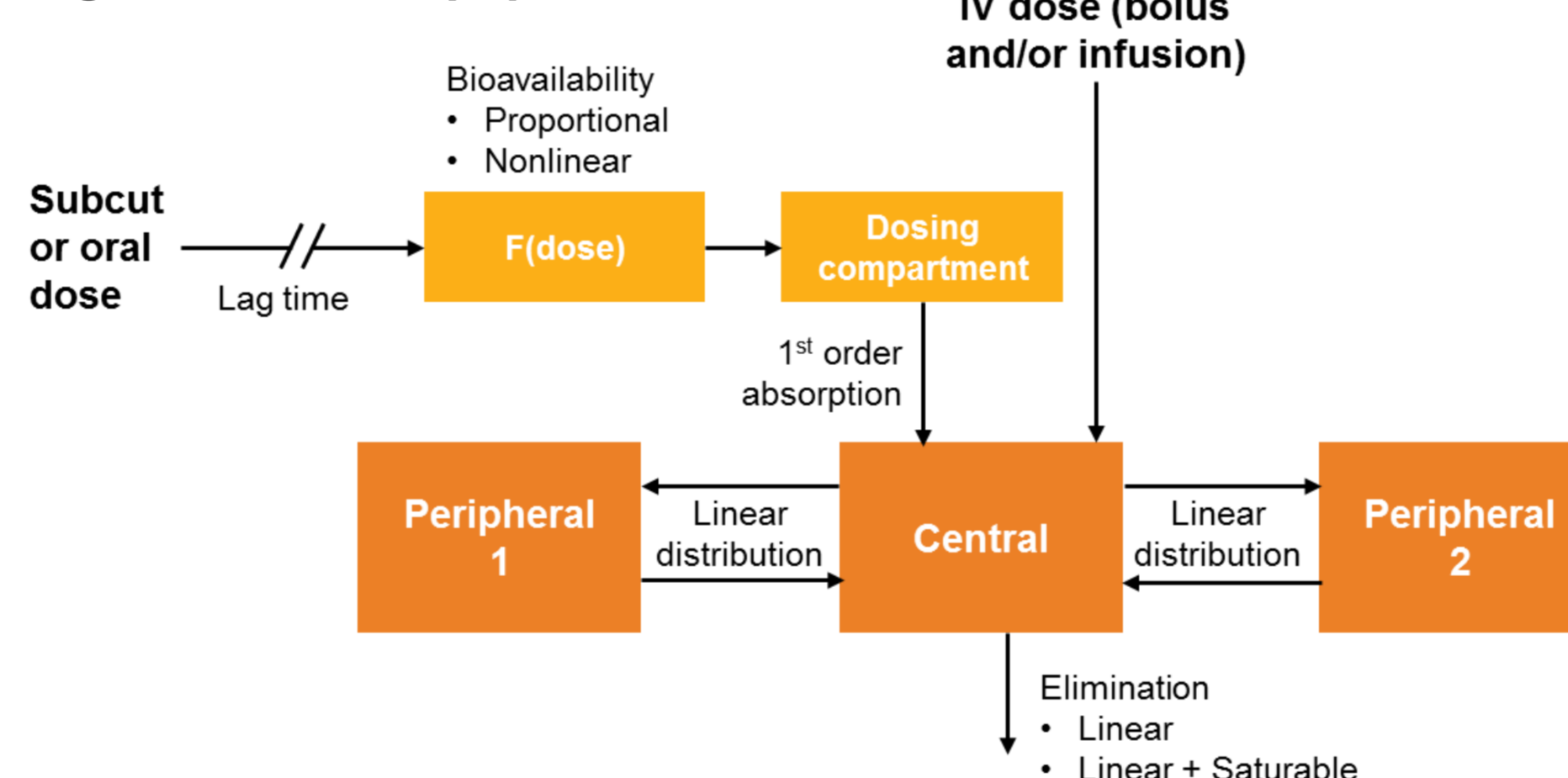
Standardization allowed for

- Efficient dataset programming
- Automatic consistency checking
- Consideration of important information, such as units for time, PK, and PD readouts
- Generation of high quality exploratory plots (incl. stratification) with validated fixed code

2) Typical popPK model space

Retrospective assessment of popPK modeling activities at Novartis led to the conclusion that the model structure in Figure 1 (details in Table 1) is able to describe >80% of typically used popPK models. Complex absorption models were out of scope.

Figure 1. General popPK model



3) Standard popPK modeling workflow

The standard popPK modeling workflow consists of the typical steps. The innovation is provided in the efficient realization of the workflow.

- Data exploration
- Data cleaning
- Base popPK model building
- Covariance model building
- Covariate model building

4) Implementation of popPK workflow

Our proposed workflow has been implemented in the SBPOP package[1]. It consists of functions and users guide on how to exploit them for specific subtasks. Each of the five steps can be accomplished using a single function call while specifying options or using defaults.

For typical popPK data a single run of each workflow step is often enough as several models/scenarios are considered simultaneously.

The modeler considers the output of the workflow at each stage and customizes the next step.

Available features supporting the modeler are

- Definition of sub-space of models to consider
- Automatic generation and running of these
- Generation of relevant goodness-of-fit lots
- Automatically stratified visual predictive checks
- Tables for comparison of pre-specified models
- Robustness assessments of selected models
- Parametric sensitivity analyses to assess probable information content of future studies

5) Test/validation of the workflow

The workflow has been tested on several projects, ranging from first-in-human studies to popPK modeling for submissions.

Table 1. PopPK model features considered in workflow tool

Feature	Options
Number of compartments	1,2,3
Parameter estimation	estimate or fix some fixed or random effects
Parameter distribution	assume log-normal distribution of PK parameters
Residual error models	additive; proportional; add+prop; exponential
Bioavailability	constant; function of dose
Absorption	first-order with and without lag time
Distribution between compartments	linear
Elimination	linear; linear+saturable
Covariance model	diagonal matrix; full matrix; selected combinations
Covariates	estimate or fix covariate coefficients

Discussion

- The proposed modeling workflow eliminates labor intensive repetitive coding tasks, allows better focus on the modeling rather than the tools used. It leads to higher efficiency and a larger degree of trust in the final model and parameter estimates.
- Standard modeling plans and reports were out of scope but could be included.
- The approach is extensible to PKPD modeling.

References:

[1] H. Schmidt. SBPOP Package: Efficient support for model based drug development – from mechanistic models to complex trial simulation, Poster, PAGE, 2013. www.sbtoolbox2.org

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