

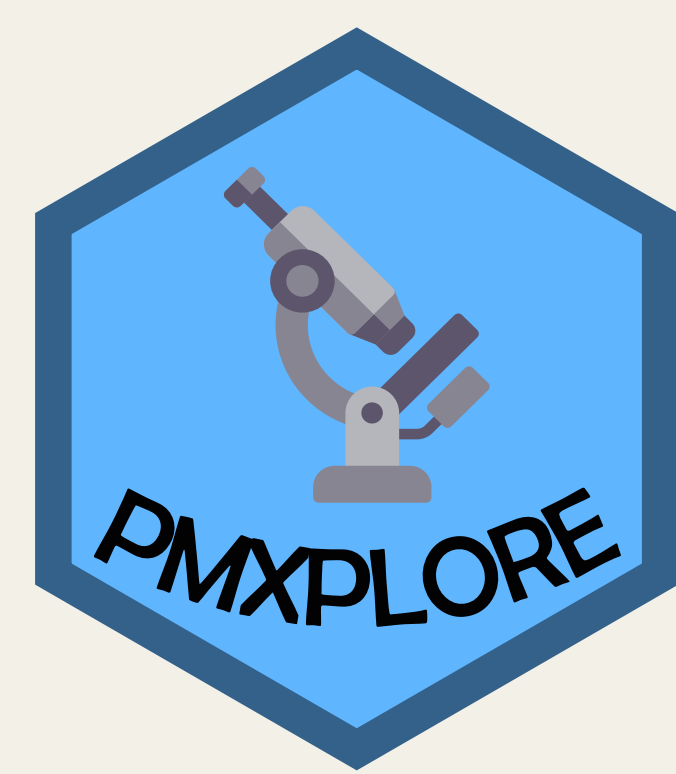
PopkinR: a suite of Shiny applications focused on the pharmacometrics workflow

Patrick Nolain¹, Romain Combet¹, David Marchionni¹, Heiner Speth², Jean-Marie Martinez¹, David Fabre¹
¹ Sanofi R&D, Montpellier, France, ² Sanofi R&D, Frankfurt, Germany



Introduction: Pharmacometrics workflow can be defined by a succession of well-defined tasks ranging from exploratory data analysis, modeling (execution, diagnostics, validation, simulation) and communication. Although each of these steps often require dedicated software and technologies, they share common needs (e.g. data visualization, reporting) which could take benefit from interactive analyses. The recent growth of data science related tools in R¹, in particular the web-application framework Shiny², brings new opportunities for the development of tools facilitating these activities.

Methods: A suite of interactive web-applications was developed to help NONMEM modelers within Sanofi in the processing of several stages of a pharmacometric analysis using R and the shiny package.



Exploratory Data Analysis of NONMEM-like datasets

Interactive visualizations and summaries of dependent variables, dosing regimens and covariates (distributions, longitudinal evolution).

Provides dataset manipulation functionalities.

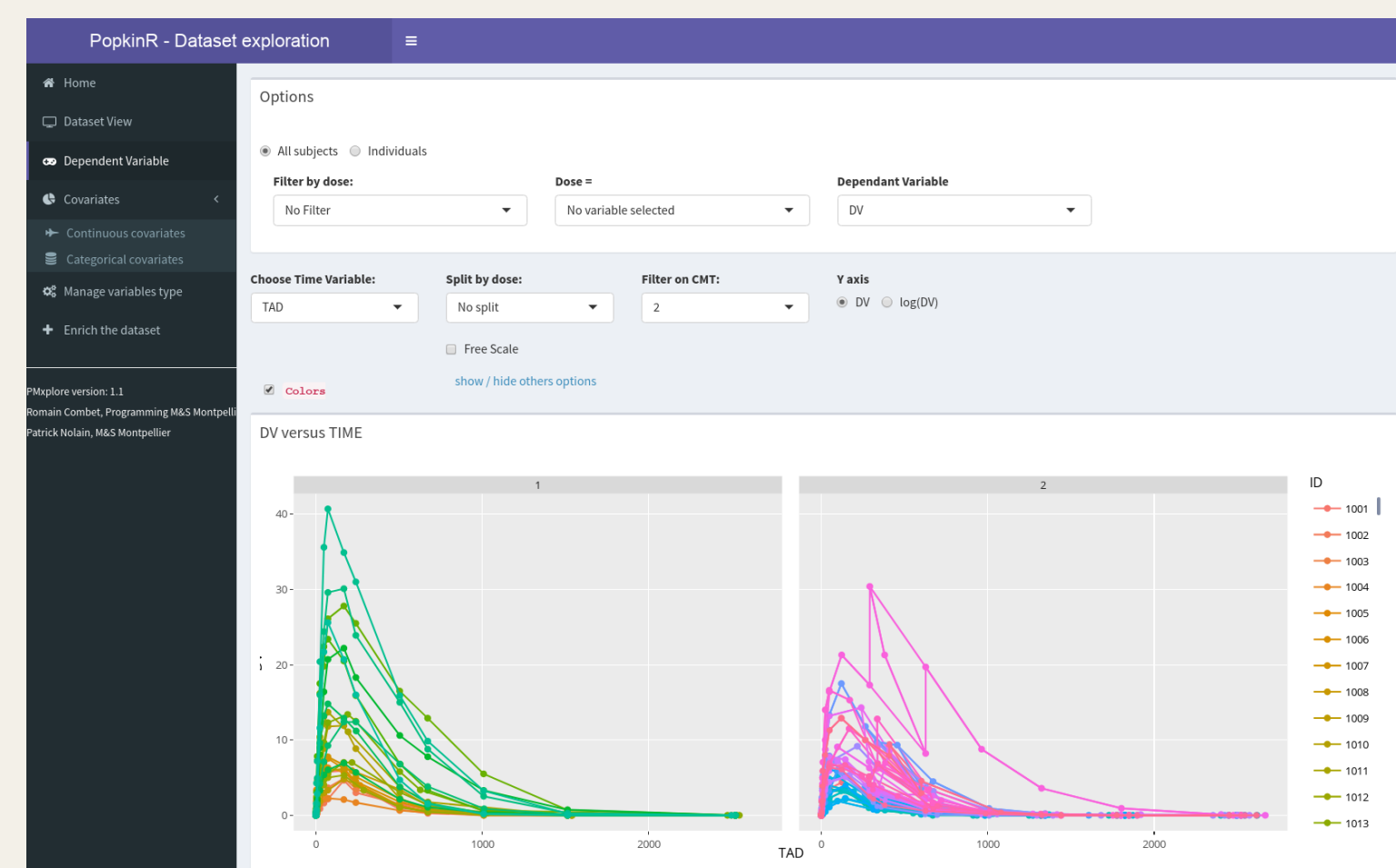


Fig. 1 - Dataset exploration with PMXPlore



NONMEM run management

Pilots the execution of NONMEM runs either on a local computer or within a PBS-based HPC infrastructure like the Sanofi Popkin³ cluster.

Generates control files for batch analysis (e.g. bootstrap, initial value search, sensitivity analysis), prior-based

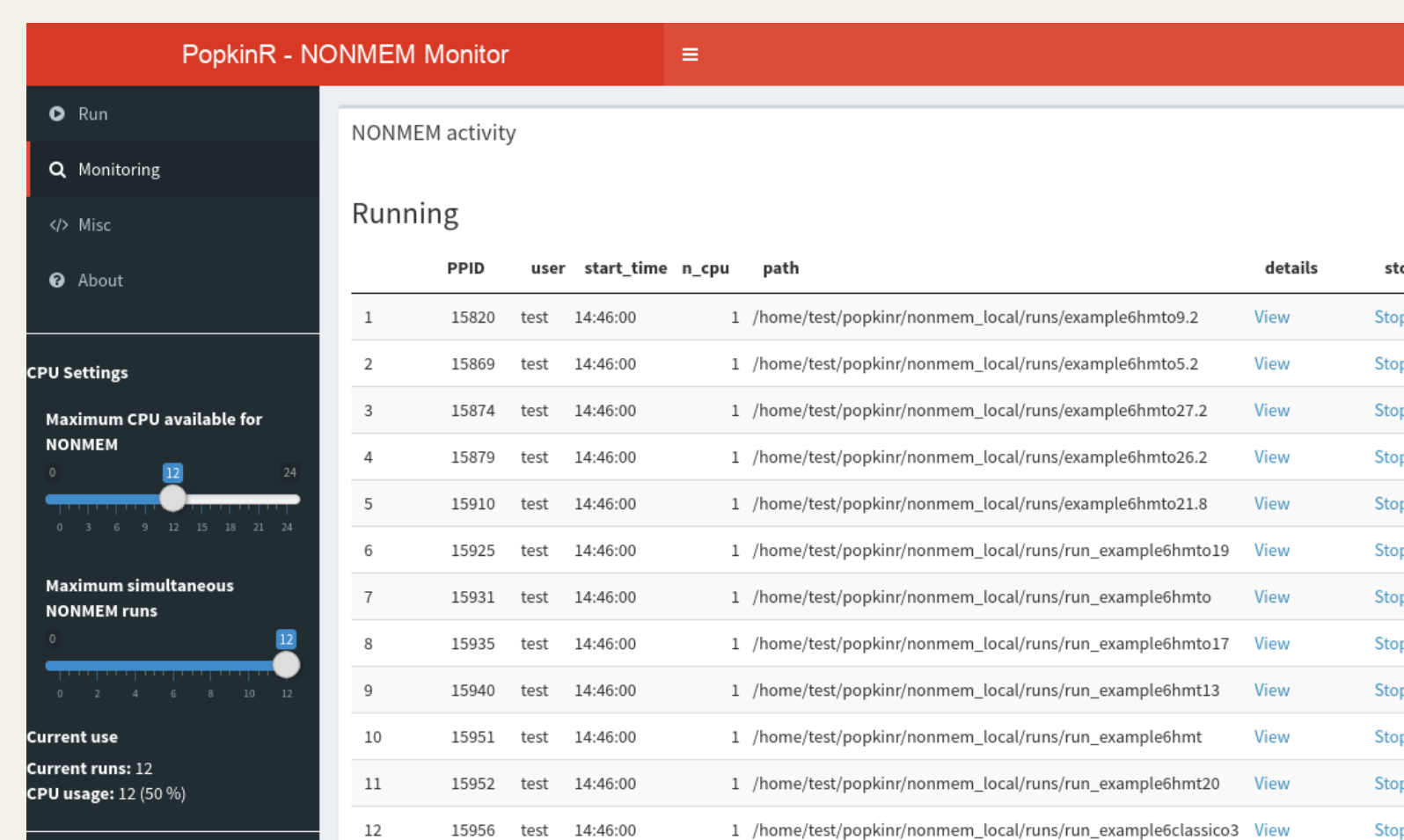
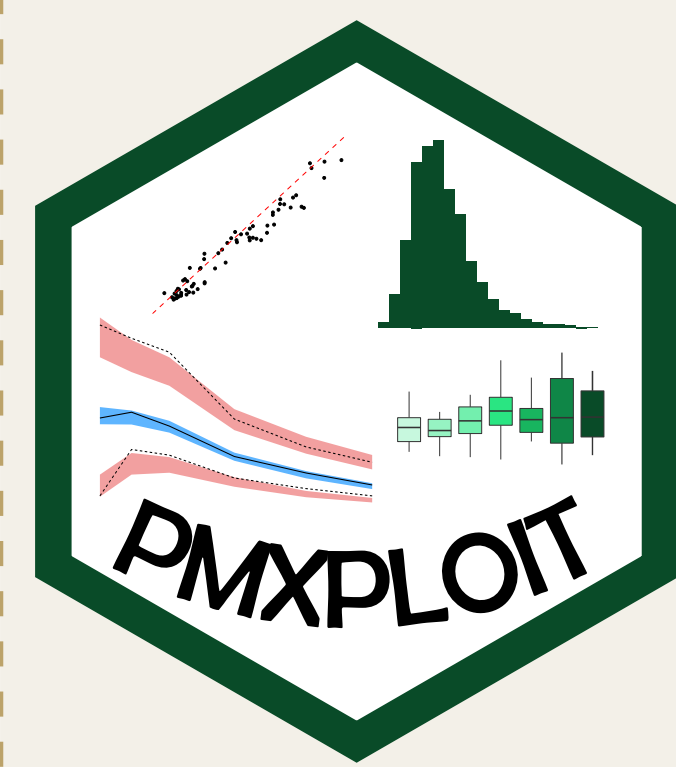


Fig. 2 - PMXrun list of running models



Fig. 3 - Parameter convergence monitoring



NONMEM post-processing analysis

PMXploit is an R package dedicated to NONMEM runs post-processing, willing to make the modeler's job easier when analyzing run results.

It provides helper functions for generating of diagnostic plots, computing statistics related to parameters and covariates, calculating numerical quality criteria or comparing multiple runs.

A shiny-based **NONMEM Toolbox** application has been developed alongside PMXploit to bring interactivity with a dynamic front-end.

A user can rapidly obtain summaries of estimation results (e.g. convergence, parameters estimates, shrinkage), generate visualizations, detect outliers or compare runs on-the-fly, improving model diagnostics and data exploration.

Generated plots and tables can easily be integrated into reports as well as splitted and filtered for subgroups analyses (e.g. goodness-of-fit by compartment, parameter distribution per gender...).

R code

```
library(pmxploit)
run <- load_nm_run("/path/to/run")

run %>%
  group_by(CMT) %>%
  plot_dv_vs_predictions()

run %>%
  group_by(SEX) %>%
  plot_parameters_distributions()

run %>%
  plot_parameters_correlations()
```

Output

Examples of PMXploit function calls

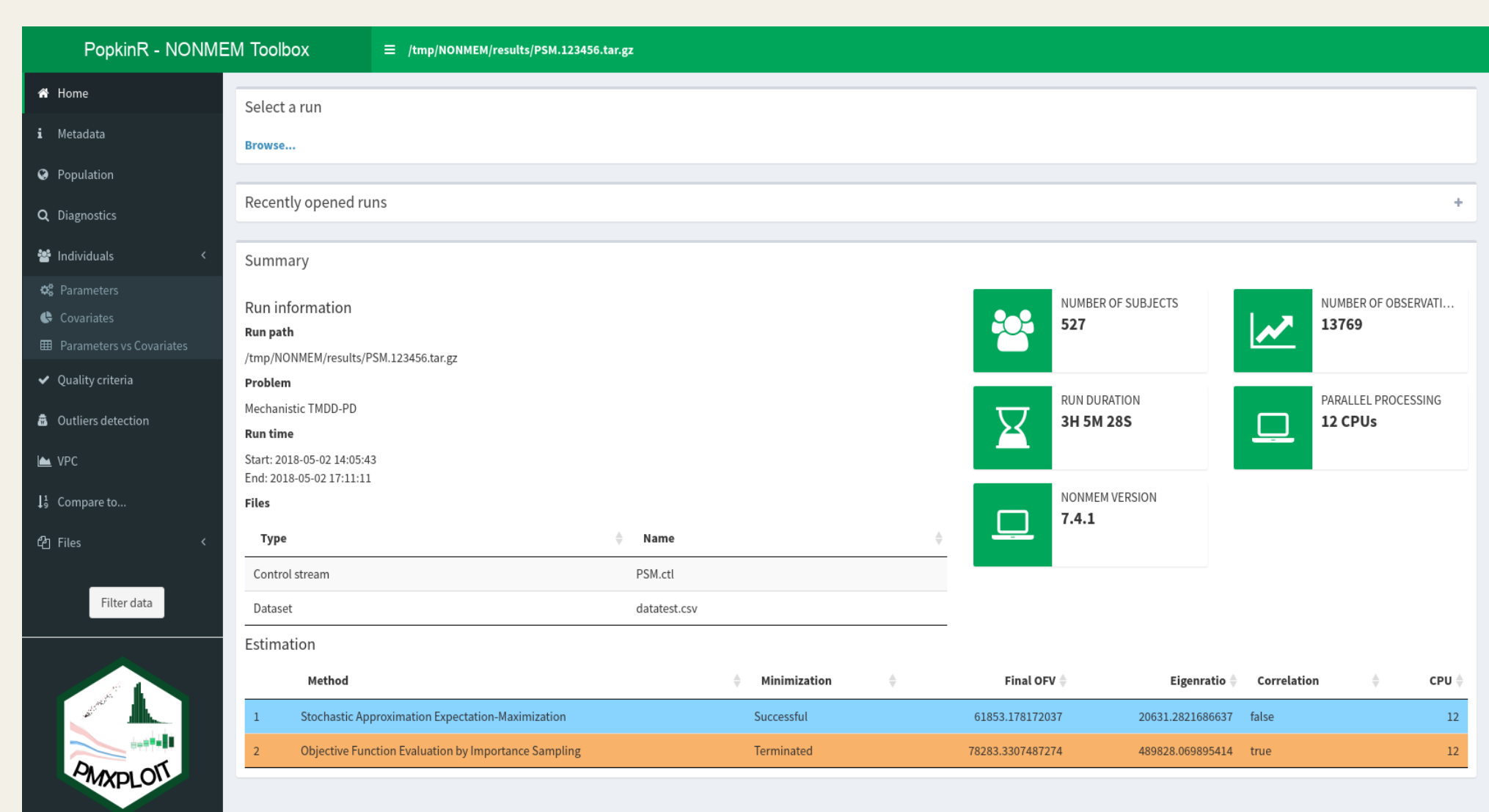


Fig. 4 - NONMEM Toolbox user interface

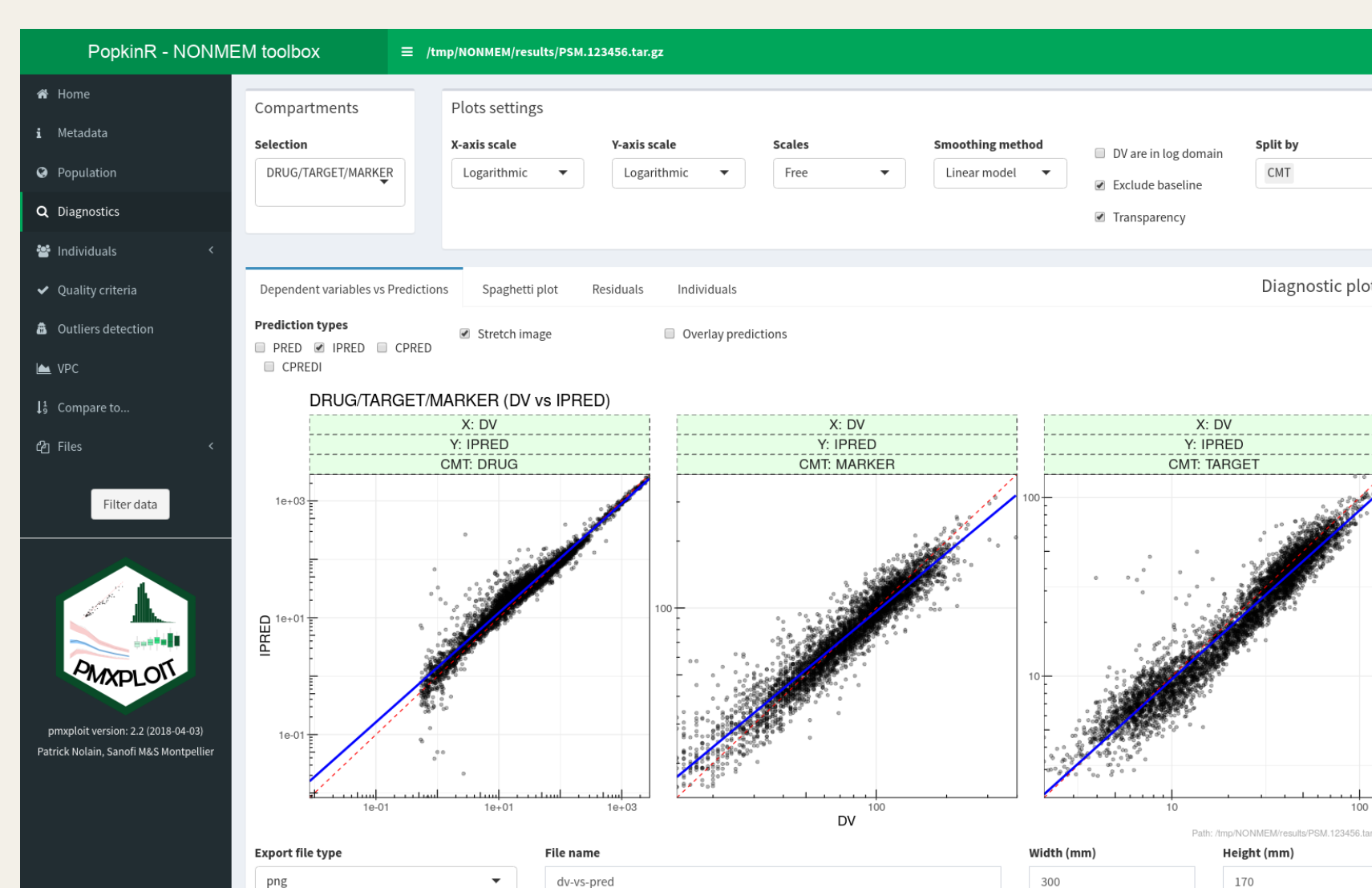


Fig. 5 - Interactive diagnostic plots

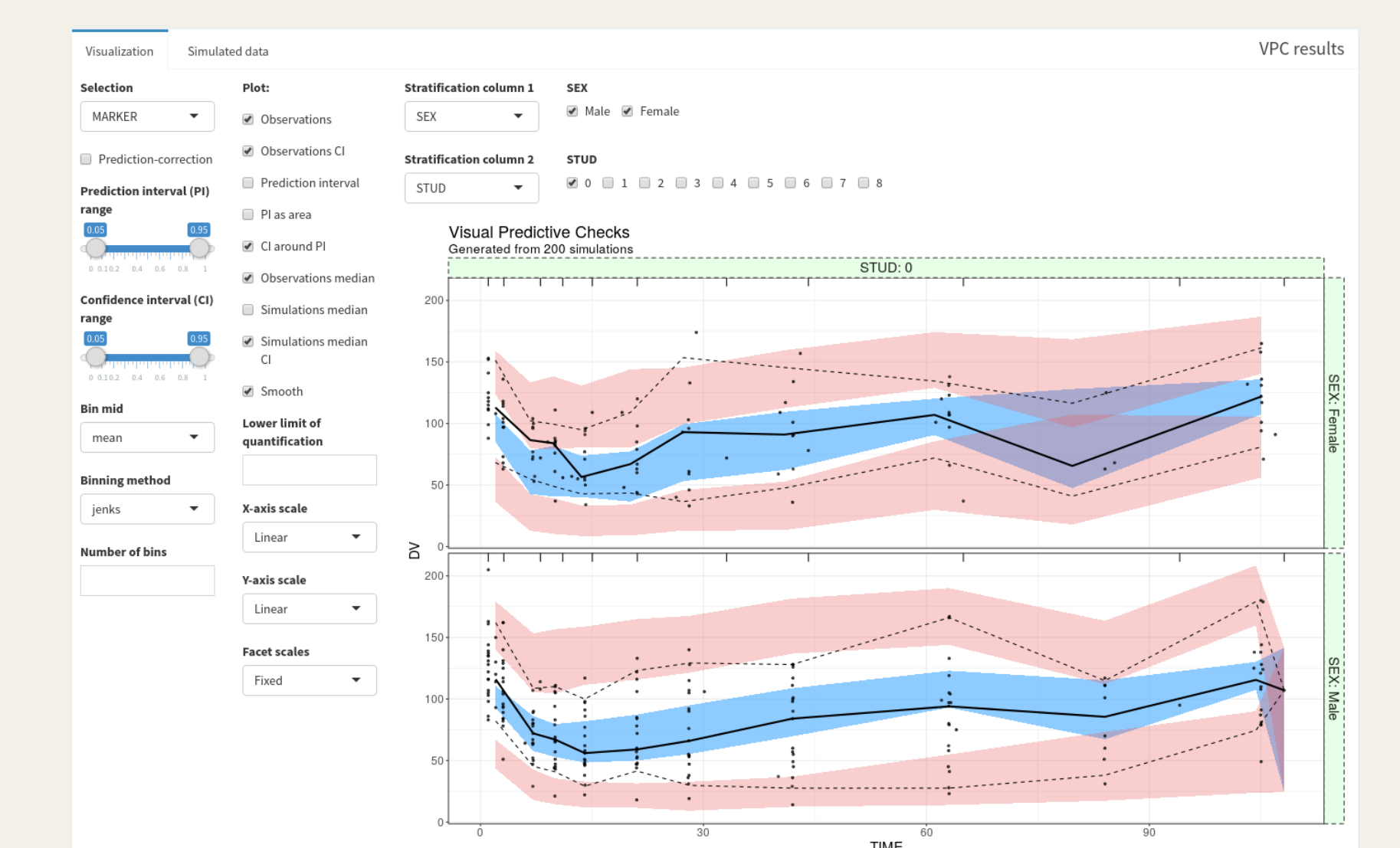
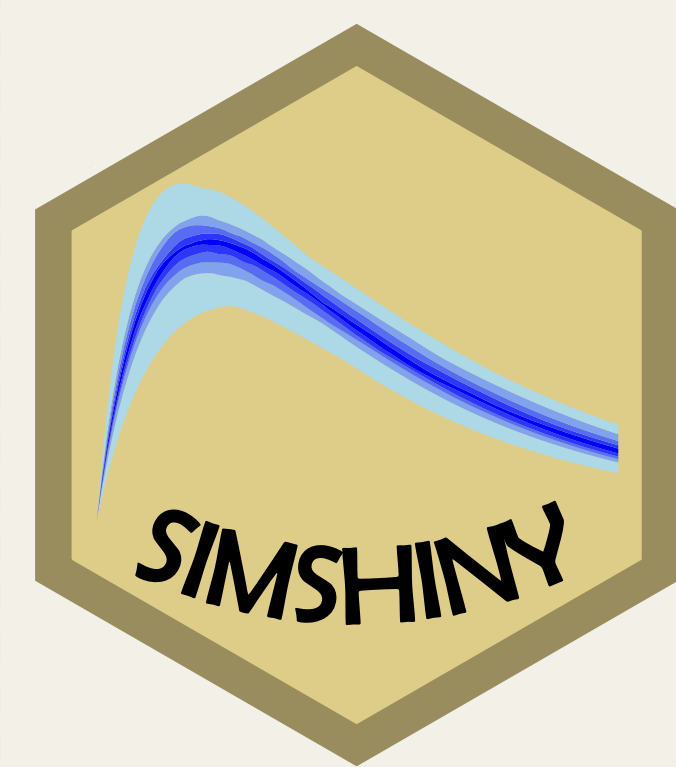


Fig. 6 - Visual Predictive Checks tab (using the vpc⁴ R package)



Dynamic model-based simulations

Interactive applications dedicated to specific projects or models.

Models developed either with NONMEM or Monolix are implemented using mrgsolve⁵, RxODE⁶ or mlxR⁷ R packages.

User interfaces are adapted to each particular situation: comparison of dosing scenarios, computation of exposure parameters, comparison to literature, exploration of complex dynamical systems or visualizing inter-individual variability.

Facilitates communication of modeling results and fosters collaboration with non-modelers, increasing the visibility of pharmacometry and its contribution to decision-making.

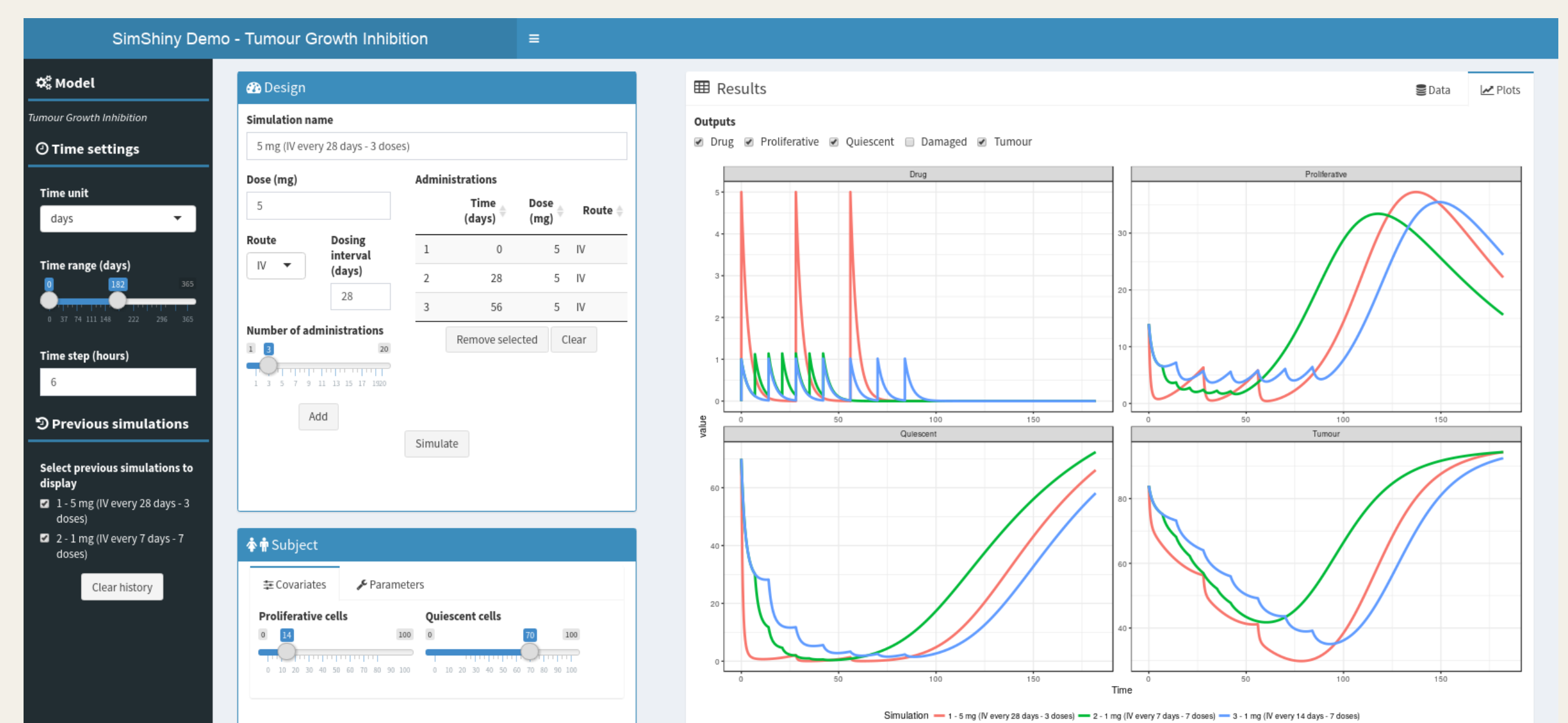


Fig. 7 - A SimShiny application comparing outcomes of dosing scenarios

Conclusion

A suite of web-applications dedicated to several steps of pharmacometrics workflow, from data exploration to simulation-based decision making, was developed. PopkinR shows the ability of interactive applications to improve the efficiency of pharmacometricians' work and the communication of modeling and simulation contribution to a wider audience to support drug development. PMXploit package and PopkinR applications source code will be publicly available as soon as possible.

References

- [1] R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. <https://www.R-project.org/>
- [2] Winston Chang, Joe Cheng, JJ Allaire, Yihui Xie and Jonathan McPherson (2017). shiny: Web Application Framework for R. R package version 1.0.5. <https://CRAN.R-project.org/package=shiny>
- [3] Speth H (2004). A Linux cluster for population pharmacokinetic analyses. International journal of clinical pharmacology and therapeutics 2004 42:3 (189-190)
- [4] Ron Keizer (2018). vpc: Create Visual Predictive Checks. R package version 1.0.1. <https://CRAN.R-project.org/package=vpc>
- [5] Kyle T Baron (2017). mrgsolve: Simulate from ODE-Based Population PK/PD and Systems Pharmacology Models. R package version 0.8.10. <https://CRAN.R-project.org/package=mrgsolve>
- [6] Matthew L. Fidler, Melissa Hallow and Wenping Wang (2017). RxODE: Facilities for Simulating from ODE-Based Models. R package version 0.6-1. <https://CRAN.R-project.org/package=RxODE>
- [7] Marc Lavielle (2018). mlxR: Simulation of Longitudinal Data. R package version 3.3.0. <https://CRAN.R-project.org/package=mlxR>

