

User-friendly and Quality-Controlled PBPK/QSP M&S Framework in R for Regulatory Submissions using the Open Systems Pharmacology Software

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Intro

The increasing importance of Physiologically-Based Pharmacokinetic (PBPK) and Quantitative Systems Pharmacology (QSP) models for regulatory submissions in drug development necessitates user-friendly and quality-controlled tools and workflows. Our goal is to develop a robust framework in R that facilitates PBPK/QSP modeling and simulation (M&S) projects with models developed with the open-source Open Systems Pharmacology (OSP) [1] software, promoting reproducibility, transparency, and automation in model development while minimizing error probability coming from maintaining complex R code.

Methods

An open-source R package {esqlabsR} [2] has been developed that utilizes the R packages from the OSP ecosystem: {OSPSuite-R} [3], {TLF} [4], and {OSPSuite.ParameterIdentification} [5]. The Quarto framework is used for the generation of Markdown/PDF reports, and the R Shiny package for the graphical user interface (GUI). All packages adhere to high transparency and quality control standards in software development and are available open-source.

Results – M&S workflow

The framework offers a user-friendly workflow for working with models developed with PK-Sim and MoBi (Figure 1). The key supported steps include:

1. Model development in PK-Sim and MoBi
2. Defining simulation scenarios. A scenario is defined by:
 - Species
 - Individual or population
 - Model parametrization (e.g., for different simulated compounds or disease states)
 - Application protocol
3. Defining figures to be generated
4. Performing sensitivity analysis
5. Running parameter identification
6. Generating (PDF and/or Word) reports from pre-defined templates

All workflows are built around the definition of simulation scenarios from a single simulation file. This approach ensures equal and up-to-date model structure for all scenarios and minimizes the risk reporting results for an outdated model version. The final parameter set is automatically supplied with the generated simulation report, ensuring full transparency and reproducibility.

The specified scenarios can be re-used in the subsequent steps of performing sensitivity analyses, parameter estimations, and generation of statistical and graphical results analyses.

Results – Graphical User Interface

The workflow is supported by a graphical user interface ShinyApp – ESQapp – that guides the user through the different steps of scenario and figures definition. Simulation results can be loaded from *.csv files and preview of figures created. All configurations are stored in JSON file format, allowing automated scenario generation directly from R.

Conclusion

The {esqlabsR} package and the ESQapp ShinyApp simplify user interaction with PBPK/QSP models developed in OSP software and offer intuitive workflows for M&S projects from model creation to report generation. The package is freely available on GitHub, and users are encouraged to share feedback and participate in its development to address the communities needs.

In the future, more workflows will be supported by the framework, such as pre-defined workflows for drug-drug-interaction simulations, pediatric scaling, or high-throughput PBPK modeling. The GUI app will be continuously developed to offer more model analyses functionalities and to allow generation of new model structure from pre-defined model blocks.



An open-source utilities package for user-friendly M&S workflows with OSPs

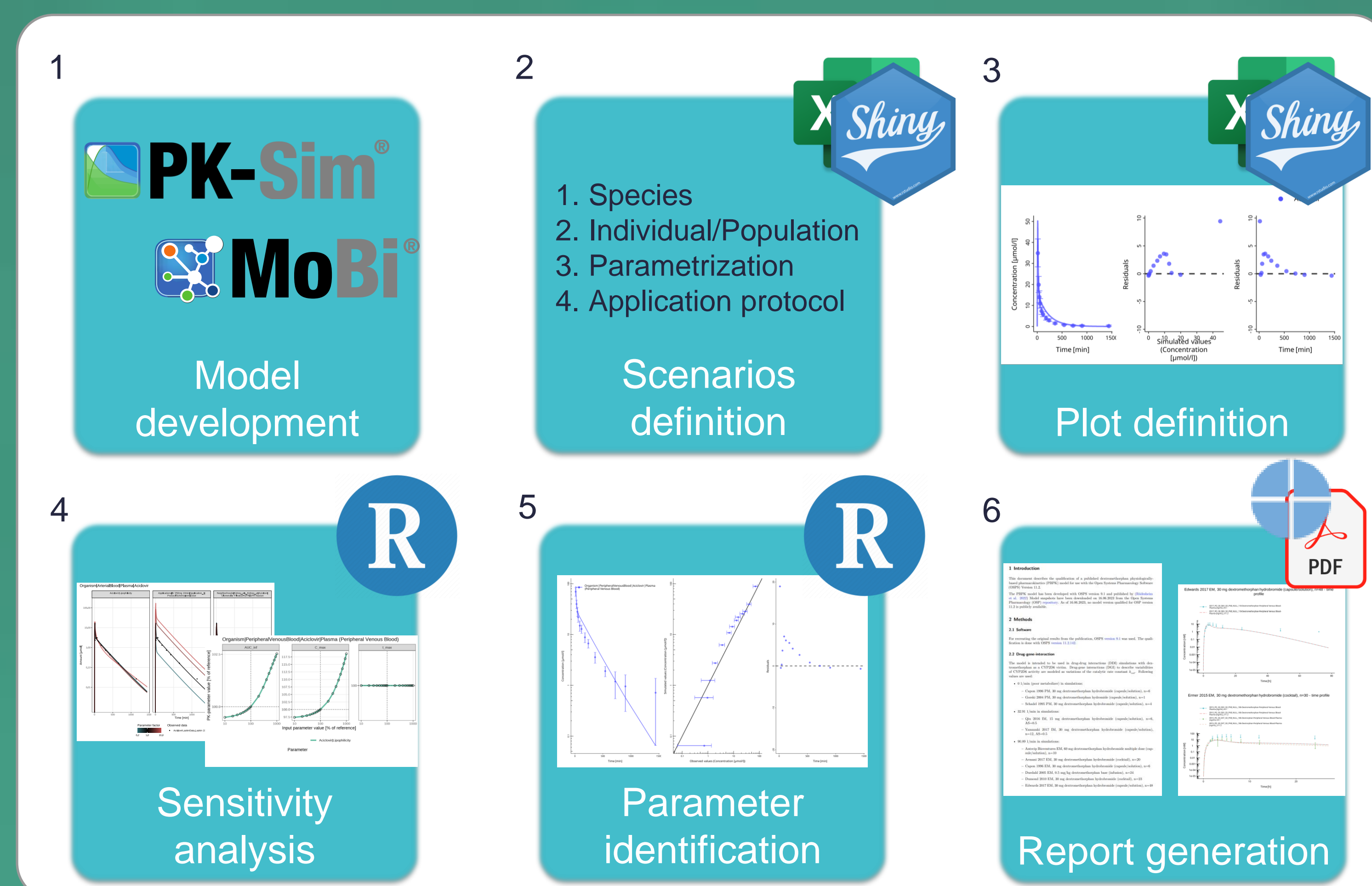


Figure 1: Typical M&S project workflow supported by the {esqlabsR} package. 1. Model development in PK-Sim and MoBi. 2. Defining simulation scenarios. 3. Defining figures. 4. Performing sensitivity analysis of the model(s). 5. Running parameter identification. 6. Generation of reports (PDF or Word file formats) from markdown/quarto templates.

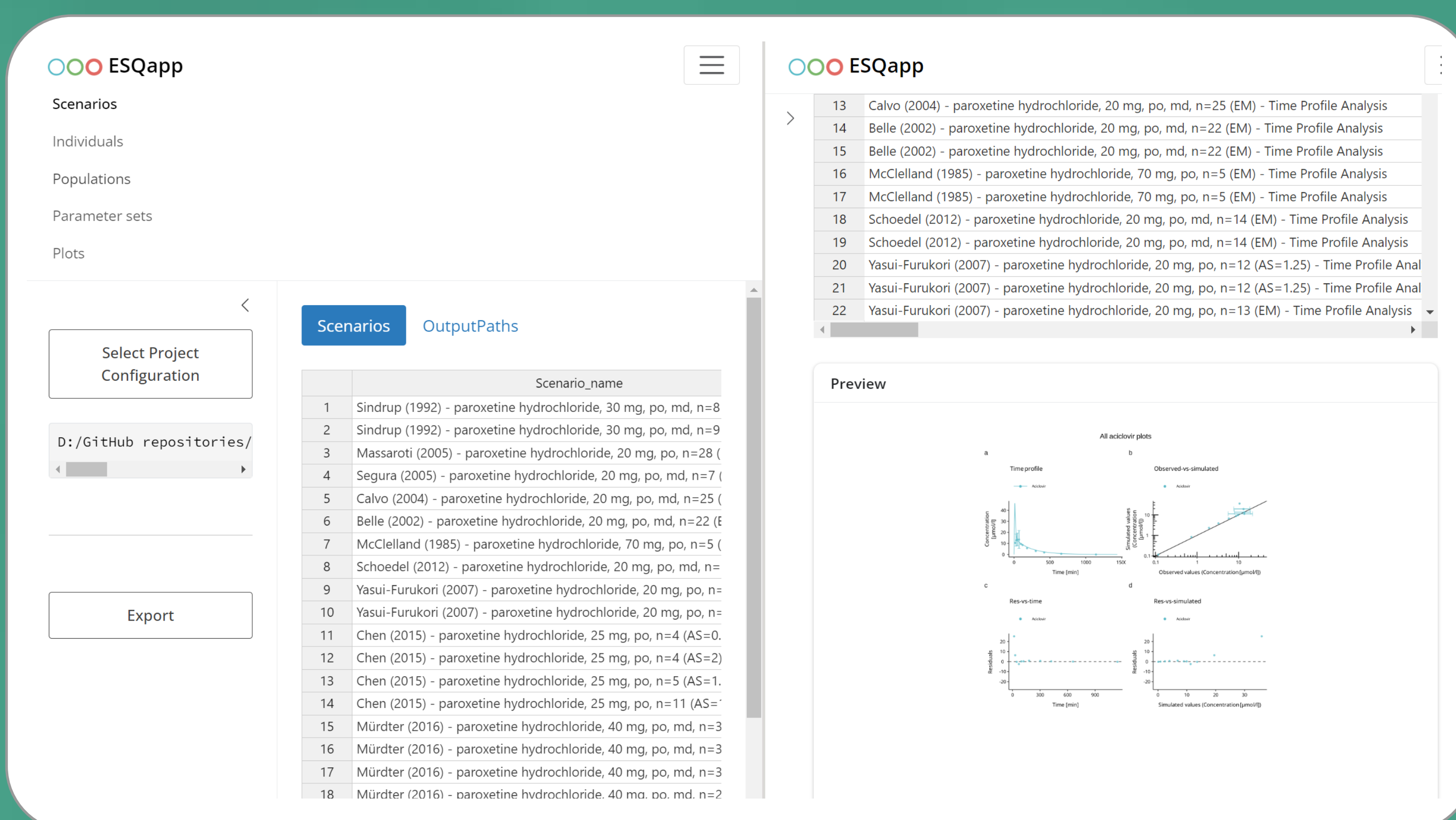


Figure 2: Graphical user interface of the ESQapp – a ShinyApp for setting up simulation scenarios, figures, and interactive plot preview (steps 2 and 3 of the M&S workflow).

References

- [1] Open Systems Pharmacology [Internet]. [cited 2024 Mar 11]. Available from: <https://www.open-systems-pharmacology.org/>
- [2] esqlabsR: ESQlabs utilities package. R package version 5.1.3, <https://esqlabs.github.io/esqlabsR/>
- [3] ospsuite: R package to manipulate OSPSuite Models. <https://github.com/open-systems-pharmacology/ospsuite-r>
- [4] TLF: TLF Library. R package version 1.5.158, <https://github.com/open-systems-pharmacology/tlf-library>
- [5] Open Systems Pharmacology Parameter Identification package. R package version 2.0.0, <https://github.com/open-systems-pharmacology/ospsuite.parameteridentification>.



Modeling



Scaling



Coding

Supporting the open-source development of:
 OPEN SYSTEMS PHARMACOLOGY Software Suite
www.Open-Systems-Pharmacology.org