High-Throughput PBPK Framework in R using Open Systems Pharmacology Software for Anti-Tuberculosis Drug Development

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Introduction

The increasing importance of Physiologically-Based Pharmacokinetic (PBPK) models in drug development and chemical risk assessment highlights the growing need to effectively use PBPK models across a **high number of compounds**. Our goal is to develop a **robust framework** in R that facilitates simulating a high number of PBPK models integrating **in vitro and in silico compound data** in an efficient manner using the open-source Open Systems Pharmacology (**OSP**) [1] ecosystem. To this end, we developed a framework to run PBPK models in a high-throughput and user-friendly approach, testing it on a sample set of **anti-tuberculosis drugs**.

Methods

Using open-source R packages from the OSP ecosystem, we developed a framework that allows **efficient configuration and simulations** of many compounds studies by leveraging the various packages capabilities.

Results

Using the capabilities of the open-source R packages from the OSP ecosystem, we developed a framework to predict the in-vivo PK profile of many drugs or chemicals. To this end, we leveraged the possibility of reusing the **same model structure** to support model reproducibility. The framework allows PK predictions in the **various species** (human, rat, mouse, monkey, dog, ...) using **different types of biological processes** (linear hepatic clearance, renal clearance, biliary clearance) as available in **PK-Sim**. To enhance usability, the pipeline can **automatically generate a generic model** incorporating the required species and processes based on defined compound properties (e.g., physicochemical characteristics, clearance mechanisms) and study design (e.g., species, administration protocol), see Figure 1. This is achieved using any PK-Sim default individuals and processes. The approach also supports the flexible integration of pharmacodynamic effects from a MoBi model by using **predefined .pkml files**.

PBPK models parameterized using physicochemical properties along with in silico and in vitro data have been reported to predict in vivo pharmacokinetic profiles, achieving AUC predictions within a 2-fold error in approximately 40% of cases [3]. We tested the framework on a sample set of **12 anti-tuberculosis** drugs that included a vast variety of administration protocols (single dose intravenous to multiple oral doses with loading doses), representing a total of **over 100 different studies** (different dose regimens and drugs) extracted from literature to ensure its usability and flexibility using QSAR predictions as inputs. On this initial set of studies focused on anti-TB drugs, we observed a simulated **AUC and Cmax within 2-fold** of the observed values for **38-42%** across all studies (AUC within 4-fold ~60% of the studies; Cmax with 4-fold in ~75% of the studies), depending on partition coefficient and cellular permeability methods chosen, see Figure 2. This seems to be in agreement with previously observed values on different datasets. The **median AUC ratio** across all studies is **0.6-fold**, while the **median Cmax ratio** is **1.3-fold**.

Highly lipophilic compounds with low fraction unbound and low solubility tend to be underpredicted by the framework, see Figure 3. For these specific compound types, further investigation and/or refinement of predicted absorption or distribution properties is needed for improved outcomes.

Conclusion

An efficient HT-PBPK framework has broad **applications** and can serve as a valuable tool to streamline drug development, it can:

- **efficiently integrate QSAR with IVIVE for PBPK**, providing quantitative PK estimates where little to no in vivo data is available
- integrate with machine learning approaches to **refine input parameter** predictions for PBPK models [2]
- facilitate retrospective analysis on large databases of compounds with available in vivo PK data, allowing **systematic evaluation** and **refinement** of modeling methodologies and **structural model hypotheses** [3].
- help **optimise and calibrate IVIVE workflows**, such as refining intestinal permeability estimates from in vitro assays

This approach has demonstrated innovative impact, with new opportunities to streamline anti-TB drug development by accelerating data-driven decision-making and improving predictive performance in the early-stage development of new compounds.

Leveraging the power of **OSP for HT-PBPK**

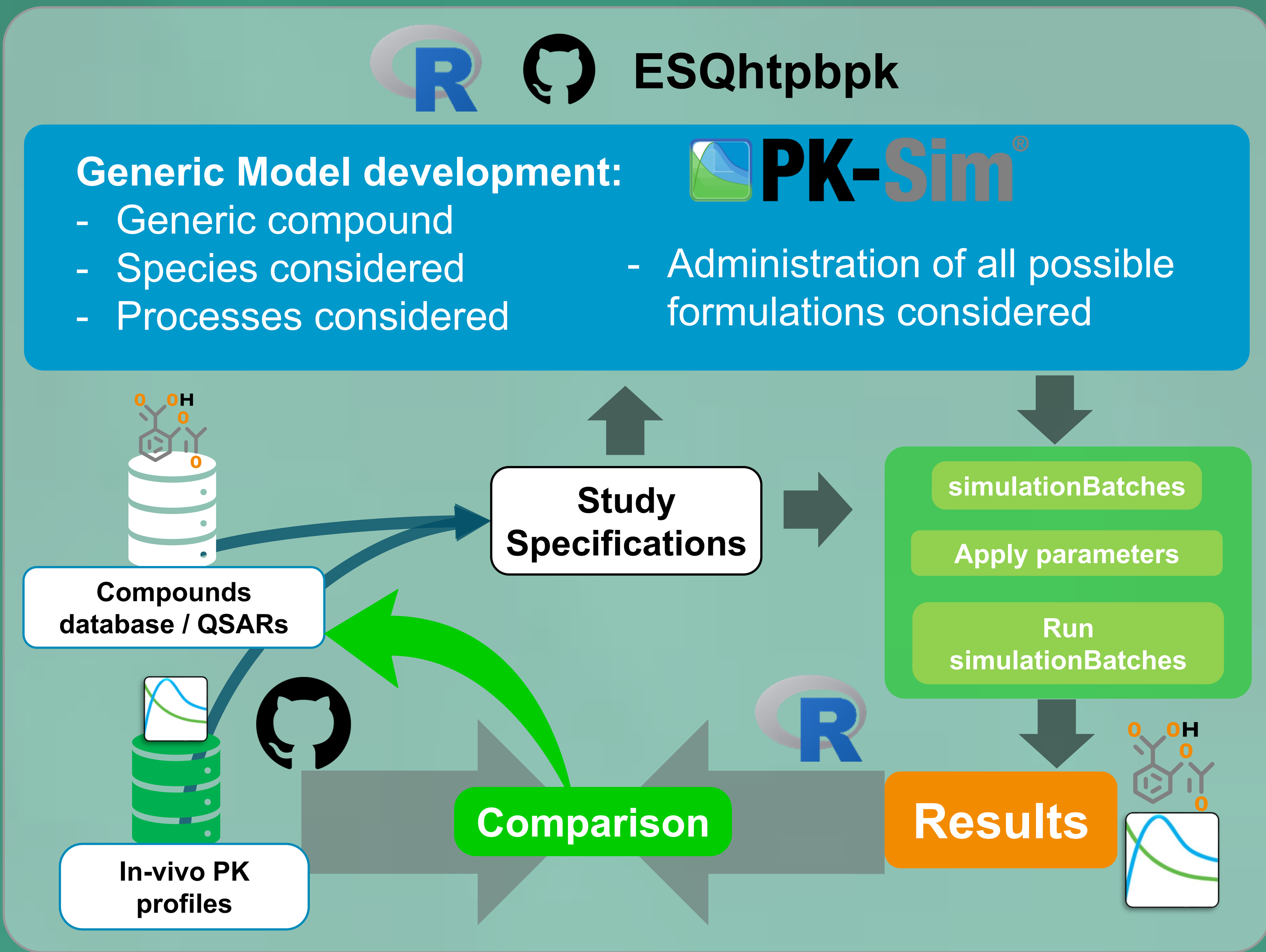

Figure 1: Workflow of HT-PBPK for in-vivo predictions

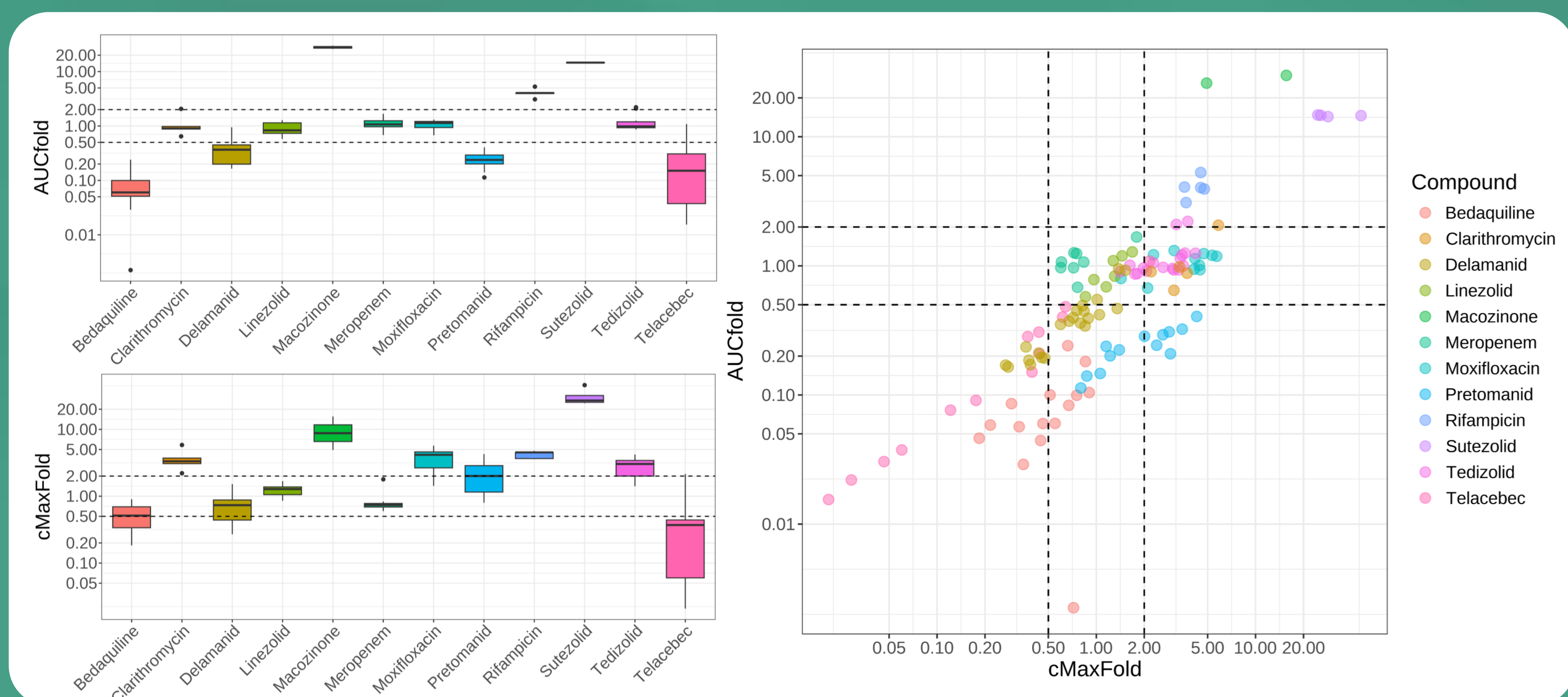

Figure 2: Predictions assessment from QSAR as input to the HT-PBPK framework of various anti-TB drugs.

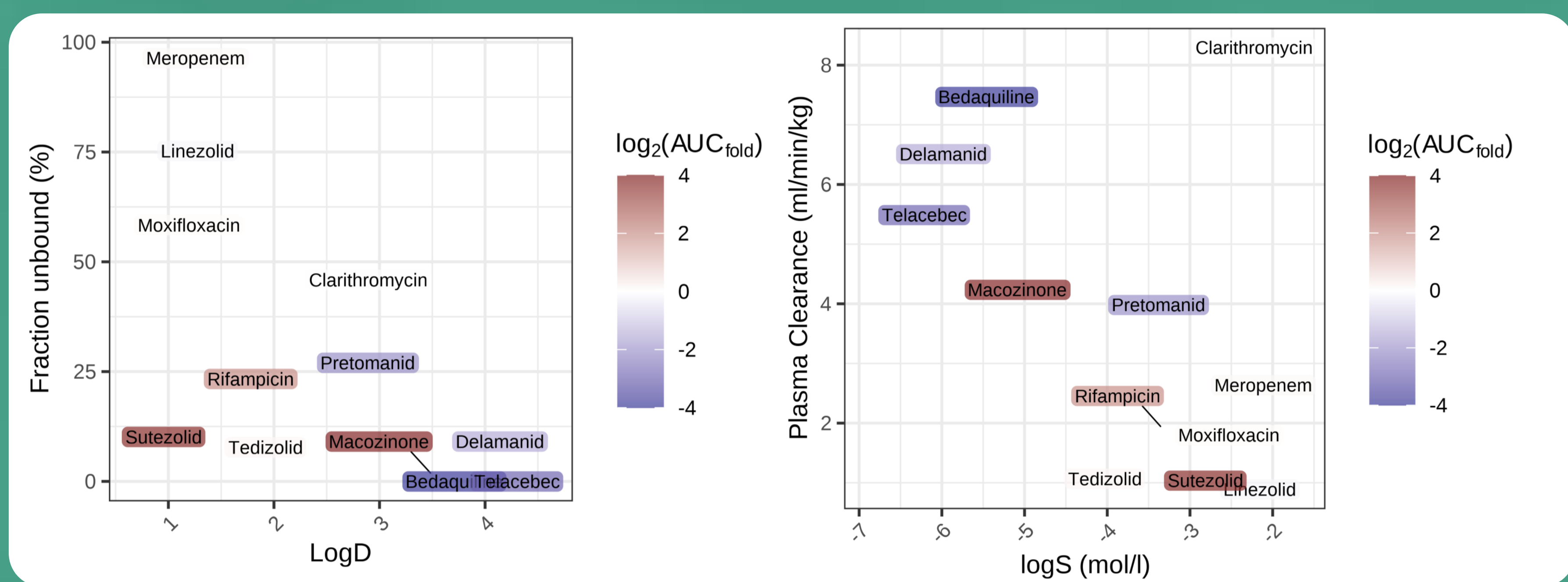

Figure 3: Main compound characteristics used as input taken from QSAR in relation to AUC fold prediction accuracy

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