

A Systems Pharmacology Approach for Translational Learning and Pharmacokinetic Predictions across Patient Populations

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Objectives: The goal of the presented work is to develop a translational approach that enables the identification and transfer of (patho-) physiological and drug-specific knowledge across distinct patient populations.

Methods: Physiological and physicochemical parameters are extracted from experimental data by a Bayesian-PBPK analysis, thereby taking into account available initial literature information [1]. The Bayesian approach in combination with mechanistic modeling enables the translation of knowledge, as the conserved underlying model structure and model parameters across populations allow the transfer of assessed parameter distributions as initial knowledge in subsequent Bayesian-PBPK analyses.

Results: In the translational approach (Fig. 1), a Bayesian-PBPK analysis is performed using study data of a probe drug in a cohort of healthy volunteers (1). Next, the physiological knowledge acquired in step one is refined in combination with study data of a candidate drug in the same cohort of healthy volunteers (2). The acquired physicochemistry of the probe drug is used with study data of a diseased patient cohort to identify pathophysiological changes in this population (3). The acquired physicochemistry of the candidate drug and the assessed pathophysiology from step three are combined for a de novo prediction of the population PK of the candidate drug in the diseased cohort (4). Notably, the Bayesian-PBPK analyses generate individual-specific information in the three learning steps and simultaneously allow to quantify the population-specific interindividual variability.

Conclusions: The presented systems pharmacology approach is a prototype for model-supported translation across the stages of pharmaceutical development programs. Potentially, it can improve the forecasting power in drug development programs by systematically incorporate and translate results of clinical trials to subsequent studies.

References:

1. Krauss, M., et al., *Bayesian Population Physiologically-Based Pharmacokinetic (PBPK) Approach for a Physiologically Realistic Characterization of Interindividual Variability in Clinically Relevant Populations*. PLoS One, 2015. **10**(10): p. e0139423.

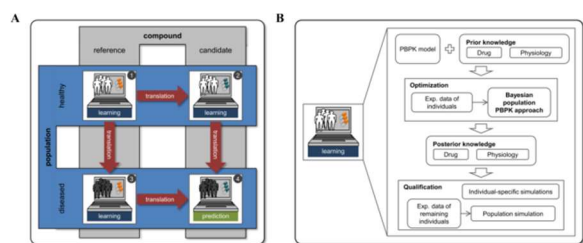


Fig. 1: Schematic illustration of the translational approach. (A) A learning step involves a full Bayesian-PBPK analysis, using initial knowledge in combination with new experimental data to refine and acquire knowledge about physiological and drug-specific parameters. A translation step transfers the acquired knowledge to a new investigation, and the acquired knowledge is used as initial knowledge in a new Bayesian-PBPK analysis. (B) PBPK model assessment for each learning step in the translational approach.