PoPKAT: A Framework for Bayesian Population PBPK Analysis

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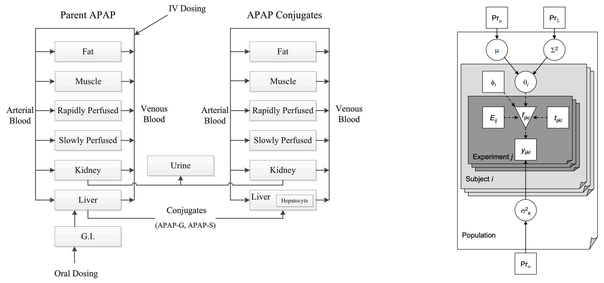
ABSTRACT

Population physiologically-based pharmacokinetic (pop-PBPK) models are powerful tools in toxicology, pharmacology, and regulatory science. One of the critical challenges in population PBPK modeling is the identification and estimation of critical model parameters at desired levels of an analysis hierarchy, from individual subject, to group, to population. Although other methods have been used for this parameterization, a hierarchical Bayesian approach is particularly well suited for this application.



Unfortunately, the adoption of Bayesian pop-PBPK modeling has been hampered by a number of factors, including difficulties in identifying influential model parameters, developing the appropriate structural and statistical models, specifying the relevant parameter priors and Bayesian likelihood distributions, and finding a simulation framework to conduct the relevant analyses. To fill this important gap, we developed **PoPKAT (Population PBPK Analysis Toolkit)**, a user-friendly, open-source platform that facilitates pop-PBPK analyses; it includes state-of-the art Bayesian sampling algorithms, parameter space reduction through global sensitivity analyses, and a graphical user interface for convenient entry of simulation information and viewing and interpretation of simulation results. Here, we detail the structure and computational capabilities of the framework and illustrate its utility for the analysis of the pharmacokinetics of several compounds of toxicological and pharmacological relevance across structural hierarchies of interest.

RATIONALE

The adoption of PBPK models has been hampered by their complexity, uncertainties in model parameters, difficulties in optimizing to individual experimental data, and lack of an integrated software platform. There is a critical need to develop a comprehensive and robust PBPK model-based approach to population PK analysis. Without such an approach, it will remain a challenge to integrate information from human physiology, chemical properties and interactions, and exposure conditions to make predictions that help ensure safety for the large and diverse populations at risk of toxicant exposure.

AIMS

Our **central hypothesis** is that a hierarchical Bayesian statistical approach using Markov Chain Monte Carlo (MCMC), when enhanced by efficiency improvements through parallelization and algorithmic changes, global sensitivity analysis (GSA), and user interface-focused features, will substantially improve both the end user experience and the accuracy, speed, and robustness of resulting model predictions.

These enhancements, while previously investigated individually, have never been combined in a population PK context}. The platform on which these enhancements will be made is `MCSim`, an open source software application ideally-suited for population PBPK analyses.

The specific aims of this study were to…

- Develop, implement, and evaluate methodologies for enhancing a thermodynamic integration-based Markov chain Monte Carlo (MCMC) algorithm for Bayesian parameter estimation in `MCSim`;
- Create, implement, and evaluate a robust Global Sensitivity Analysis algorithm to reduce PBPK model parameter dimensionality; and
- Design, build, and test `PoPKAT`, a user-friendly, open source computational platform that incorporates the above advances and provides an integrated approach for population PBPK modeling.

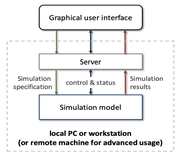
DESIGN AND METHODS

Functionality

`PopKAT` was designed to have the following capabilities:

- `User` interaction through a graphical user interface: inputs with validation, simulation control, output inspection, plotting, and storage
- Simulation types: Forward dosimetry, Monte Carlo analyses, parameter estimation through Markov chain Monte Carlo sampling, global sensitivity
- User-definable models using the `MCSim` domain-specific language, and access to previously-developed models
- Open source (code and documentation will be available in Gitlab)
- Import of pharmacokinetic data from csv and NONMEM files

Architecture



So that the computationally-expensive calculations could be run on a separate machine from the interface, `PopKAT` was designed and implemented as a client-server application. The format for communication between components and file serialization is `json`, a lightweight data-interchange format. The graphical user interface was written in C++ and QT, an open-source widget toolkit for creating cross-platform graphical user interfaces. The server, file conversion utilities, and analysis and plotting code is written in Python v3.6, using a number of associated packages, including numpy, plotnine, rpyc, pandas, jinja2.

Computational capabilities

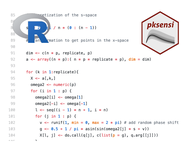
Statistical and dynamic models

The computational engine of `PoPKAT` is `MCSim` [1], an open source simulation package that allows users to design and run a variety of differential equation-based simulation models. It has been used extensively to run and parameterize PBPK, population PBPK, and hierarchical population PBPK models (see, e.g., [5,6,7]).

Under the development umbrella for `PoPKAT`, `MCSim` has incorporated the significant advances in thermodynamic integration (TI) Markov chain Monte Carlo sampling by Bois et al. [2]. These advances obviate the need for multiple chains in MCMC simulations and can sample from sharp multi-modal posteriors. In addition, through the use of appropriate 'perks' and auxiliary temperatures, TI MCMC can bridge the joint prior and the posterior distributions, and allow the calculation of normalized densities and of Bayes factors for model comparison.

Global sensitivity

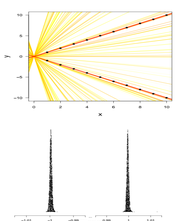
As part of the `PoPKAT` framework, a global sensitivity analysis (GSA) methodology was developed by Hsieh and coworkers [3] to reduce the dimensionality of the parameter space for PBPK models. By using this approach, which has now been implemented as a package in the R programming language [4], influential and non-influential parameters can be identified and the latter set can be neglected when estimating parameters for complex models.



RESULTS

MCMC sampling methodologies

Improved MCMC sampling through simulated tempering was evaluated for a number of models [2]. One challenging test of the improved sampling methodology is a Bayesian linear regression, but applied to an artificially pathological dataset, where the data are a mixture of two linear components (top figure). TI MCMC results in the correct bimodal distribution (bottom figure), but neither standard Metropolis-Hasting (MH) MCMC nor Hamiltonian MCMC were able to yield samples from the full posterior with only one simulated Markov chain

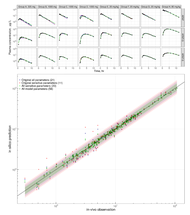


RESULTS (continued)

Also tested was the complex PBPK model for acetaminophen (APAP) from Zurlinden and Reisfeld [6,7]. This model consisted of 44 differential equations, 58 parameters, and individual and population data for calibration and testing from 21 separate studies. For reference runs with MH MCMC sampling, 10 chains of 300,000 simulations each were needed to obtain convergence. Each chain took between 26 and 34 hours to run (amounting to 330 hours of total computing time). With TI MCMC, finding an adequate schedule of 24 perks, including perk zero, required 6 hours of computing time and an additional 100,000 iterations took 11 hours to complete. **Overall to achieve the same level of accuracy in parameter estimation for the APAP model, the TI algorithm required only 5% of the computational time of that required using the traditional MH MCMC method.**

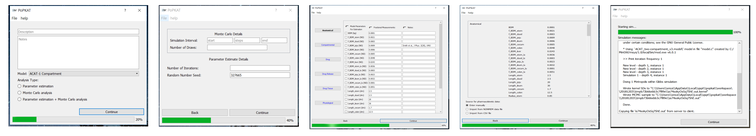
Parameter reduction

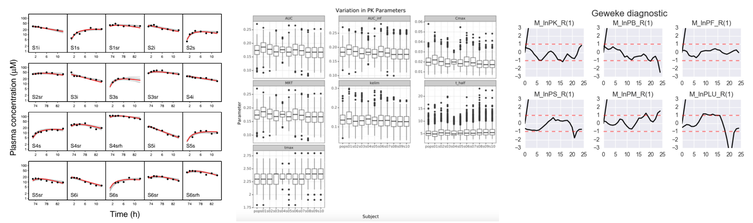
The GSA method developed by Hsieh *et al.* [3] has been used to evaluate parameter space reductions for a number of PK and PBPK models. Again considering the APAP PBPK model, in was determined that only 21 out of the full 58 model parameters were influential. **Utilizing this reduced parameter set resulted in only a very small loss of model accuracy, but a compute time of 40% of that using the full parameter set.**



Graphical user interface

Below are screenshots of several of the input screens of the `PoPKAT` user interface and some of the output plot types available, including multi-panel pharmacokinetic traces, parameter variability through box and whisker plots, and convergence diagnostics.





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