Simulation re-estimation and Bayesian Optimal Design for Population Pharmacokinetic Studies

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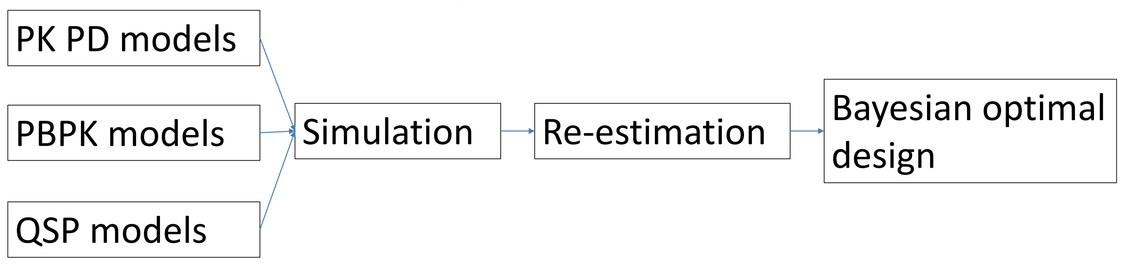
Abstract

This work finds a more robust and efficient optimal design methods to evaluate population pharmacokinetics samples, to overcome too many parameters from physiologically-based pharmacokinetic (PBPK) models or quantitative system pharmacology (QSP) models and hence to avoid identifiability problems. The Bayesian method reduces simulation and re-estimation processes for optimal design and avoids the local optimization problems.

We formulated the pop-PK optimal design in a Bayesian setting. The utility function rooted in information theory is equal to the relative entropy – Kullback-Leibler (KL) divergence from the posterior to the prior. Each design is created as an utility function. Nonparametric method was used to optimize the designs. The pop-PK models, including compartmental models, PBPK models and pediatric models are used to evaluate the algorithms.

Background

In order to avoid the identifiability problems in more complex models such as PBPK or QSP or compartmental PKPD models, simulation and re-estimation is used before the Bayesian optimal design process.



In simulation step, intensive PK samples were taken from PBPK or compartmental PK models simulation. In the re-estimation step, simplified compartmental models were built using these intensive PK samples and empirical parametric EM algorithm.

Methods

Each PK sample is used as a support point to calculate expected utility in Bayesian optimal design [1]. The Bayes' rule

$$p(\cdot\,|y,d) = \frac{p(y|d,\eta,\delta^2)p(\eta|d,\theta,\Omega)}{p(y|d,\theta,\Omega,\delta^2)}$$

Where d is the design, $p(\eta|d,\theta,\Omega) = p(\eta|\theta,\Omega)$ for the prior not vary with d.

The expected utility $\mathrm{U}(d)$ is

$$U(d) = \int_y^{\cdot}\int_\Theta^{\cdot} u(d,y,\eta)p(\eta|d,\theta,\Omega)p(y|d,\eta,\delta^2)d\eta dy$$

Where $u(d,y,\eta) \equiv D_{KL}(p(\cdot\,|y,d)||p(\cdot))$ is the utility function from the Kullback-Leibler (KL) divergence from posterior to the prior for calculating the sensitivity of each support point to finalize the expected design.

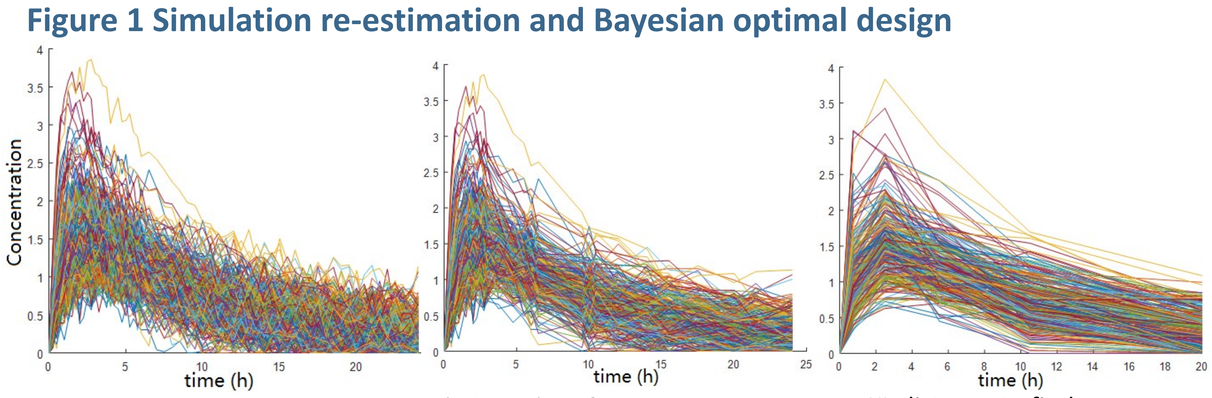
$$\mathrm{U}_i(d,\pi) = \int_\Theta \sum_{j=1}^{m} \pi_j \int_{y,\neq j} u\left(d_{\neq j}, y_{i,\neq j}, \eta\right) p\left(y_{i,\neq j}\middle| d_{\neq j}, \eta, \delta^2\right) dy p(\eta|\theta,\Omega) d\eta$$

We reused those Monte-Carlo population estimation numerical samples j in re-estimation step for Bayesian optimal design. Nonparametric method [2] is used to effectively reduce the number of support points, i.e. to remove those less sensitive/important sample points, where m is the number of support points.

Results

Bayesian optimal design using nonparametric method was successfully used for PK sampling design and optimization. The method reduces the intensive PK samples of 300 subjects simulation from 100 intensive samples over 0~24 hours (Figure 1a) to 5 sample points (Figure 1c).

Figure 1 Simulation re-estimation and Bayesian optimal design



a. Intensive samples

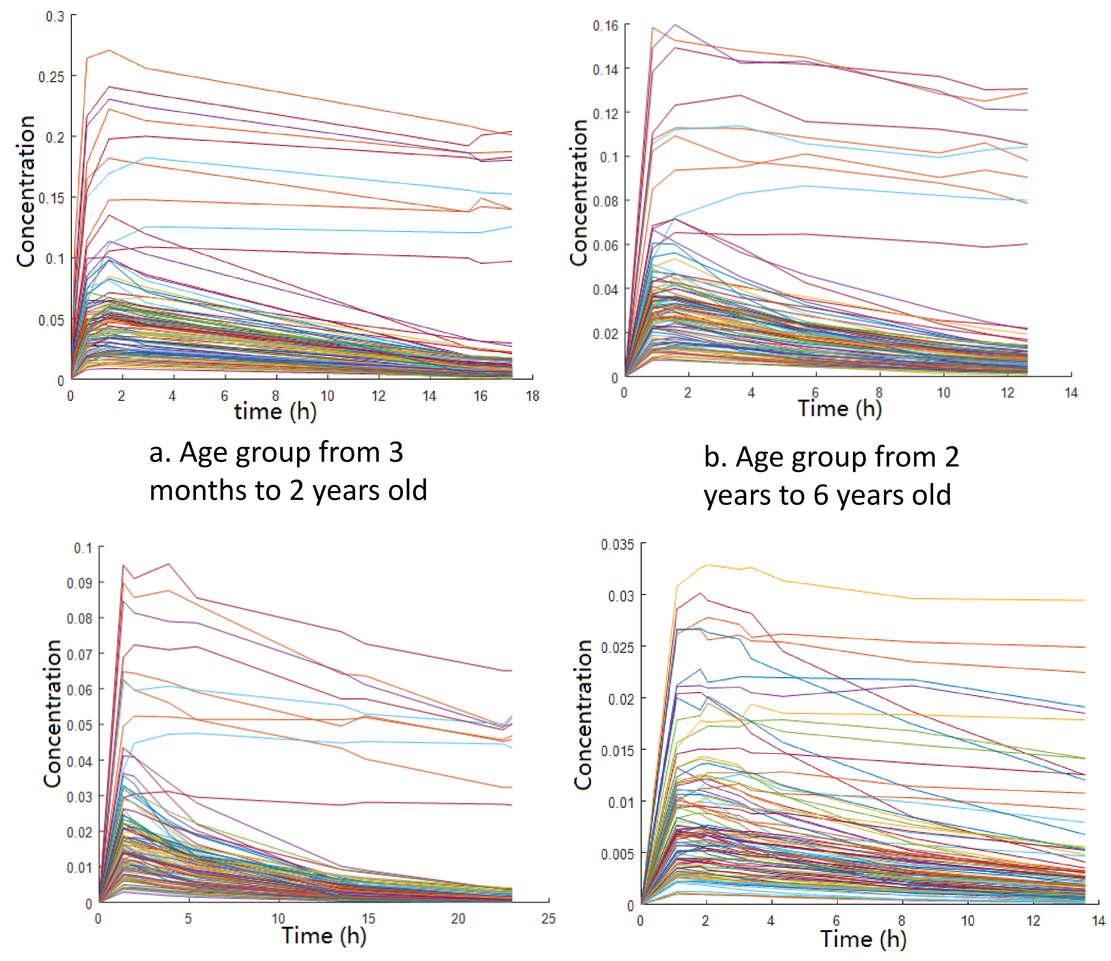
b. Samples after nonparametric method

c. KL distance to find expected design

Results (Con't)

Pediatric models are created using PBPK models in Simcyp Simulator V16 . In each age group, 100 subjects were simulated and the simulation outputted 200 intensive samples points over 0~24 hours for each individual. A simplified compartmental PK model is created using these simulation outputs from PBPK models. The Bayesian optimal design then re-use the Monte-Carlo samples from the re-estimation step to calculate the expected utility. The nonparametric method is used within the Bayesian optimal design process.

Figure 2 Suggested Samples from different Pediatric age groups



a. Age group from 3 months to 2 years old

b. Age group from 2 years to 6 years old

c. Age group from 6 years to 12 years old

d. Age group from 12 years to 25 years old

Nonparametric method reduces 200 intensive samples to a few sample points (Figure 2). The results show that the optimal sample points provide theoretical supports in sampling strategies for different age groups.

Conclusions

The work is useful because it eliminates the need to re-create the complex models such as PBPK models. It seamlessly integrates the outputs of any PKPD compartmental models, PBPK or QSP models together within the optimal design framework.

We only need the pop-PK simulation and re-estimation once from the original model to avoid the back and forth simulation and re-estimation process in each sampling design. The reuse of Monte-Carlo population estimation samples at Bayesian optimal design step reduces the computation time. The nonparametric method [2] used within the Bayesian optimal design process is fast and efficient to find the best set of samples. This method can quickly provide samples from any sampling window.

Here we used the Kullback-Leibler divergence from posterior to the prior for the design in the utility function. However, the utility function $u(d,y,\eta) \equiv D_{KL}(p(\cdot\,|y,d)||p(\cdot))$ can be flexible to many other design criteria e.g. designed AUC vs. expected AUC or designed Cmax vs. expected Cmax in any clinical trial design analysis. This method brings in theoretical support in clinical trial simulation/design by using optimization algorithms rather than manual trial and error by users.

References

- [1] Huan X. Marzouk Y. Simulation-based optimal Bayesian experimental design for nonlinear systems. J. Comp. Phys., V232 (1), P288-317, 2013
- [2] Wang Y, Maximum likelihood computation for fitting semiparametric mixture models, Stat Comput. 20: 75–8, 2010

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