PopED lite

an easy to use experimental design software for preclinical studies

In drug discovery, accurate and precise estimation of drug potency from *in vivo* data is crucial to select the right compound and to predict the human dose. Proper design of experiments is a fundamental requirement to obtain such estimates. Through this work, we wish to investigate how optimization of the experimental design can be utilized in compound selection studies, and then generalize our findings with a Matlab based software tool dedicated for drug discovery applications to automate and accelerate the experimental design optimization processes.

PopED lite was developed iteratively in a collaboration between industry and academia

AstraZeneca R&D, Sweden

Identified PK and PD models and rough estimates of the model parameters from *in vitro* studies.

PK and PD models + model parameters →

← Theoretically optimal design

Modified the theoretical optimal design considering the experimental constraints and **Conducted** the experiment.

Modified design + Experimental results →

Designed ongoing compound selection *in vivo* preclinical studies using PopED lite.

PopED lite →

feedback →

Uppsala University Pharmacometrics Group

Translated the optimal design problem to a constraint optimization problem and solved using PopED[1].

Evaluated the modified design and **Reformulated** the optimal design problem to an optimization problem with linear inequality constraints.

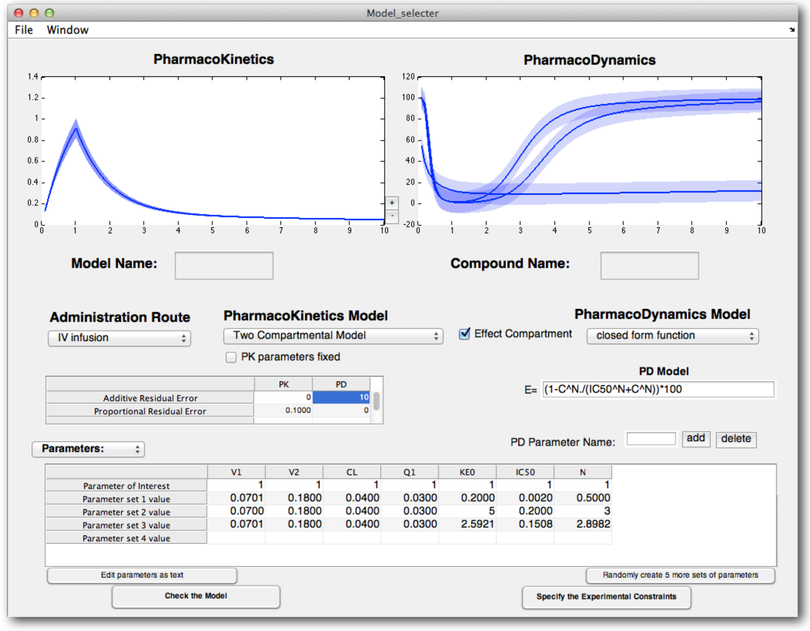
Produced PopED lite, a Matlab based software with rich graphical user-interface to solve the reformulated constrained optimization problem.

Reformulated constraints →

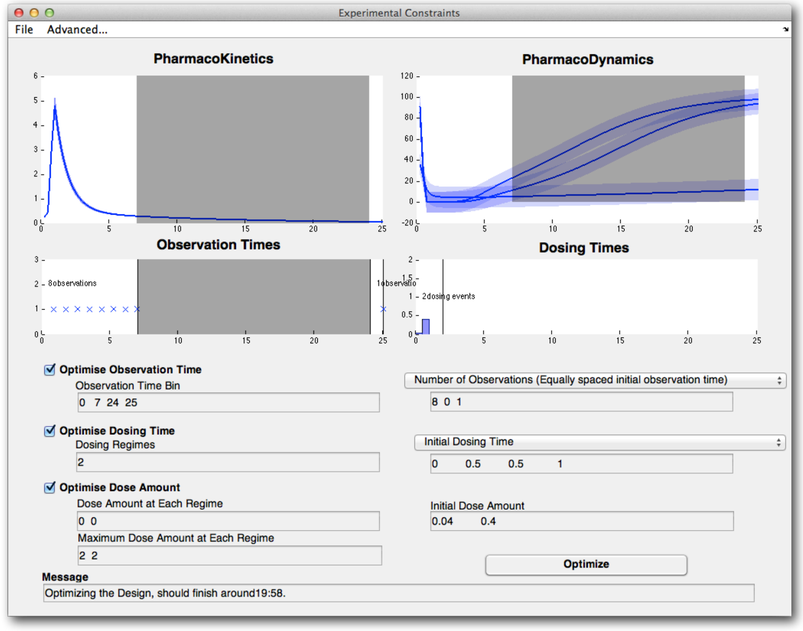
[1] Nyberg, J., et al. PopED: An extended, parallelized, nonlinear mixed effects models optimal design tool. Computer Methods and Programs in Biomedicine, 2012. In Press.

How to use **PopED** lite

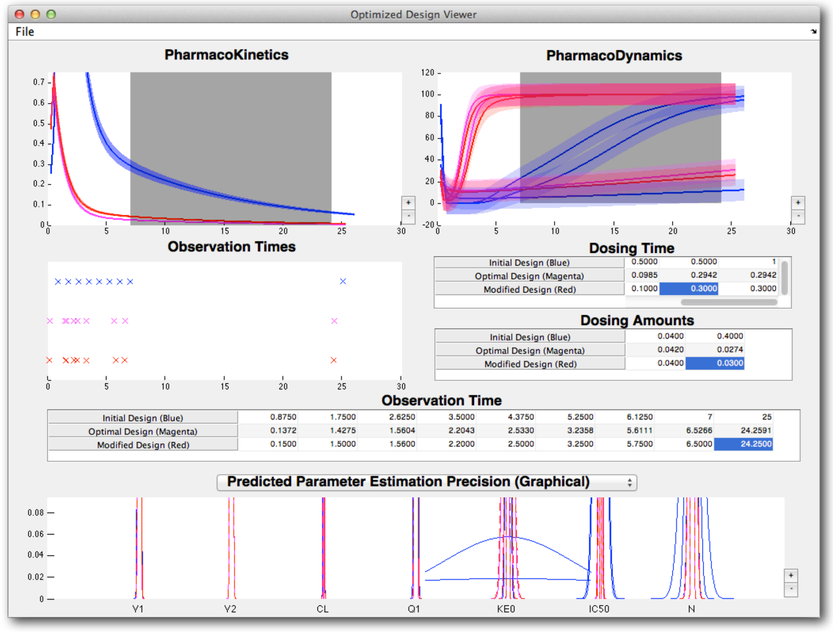
Step1: Select a Model



Step2: Specify the experimental constraints

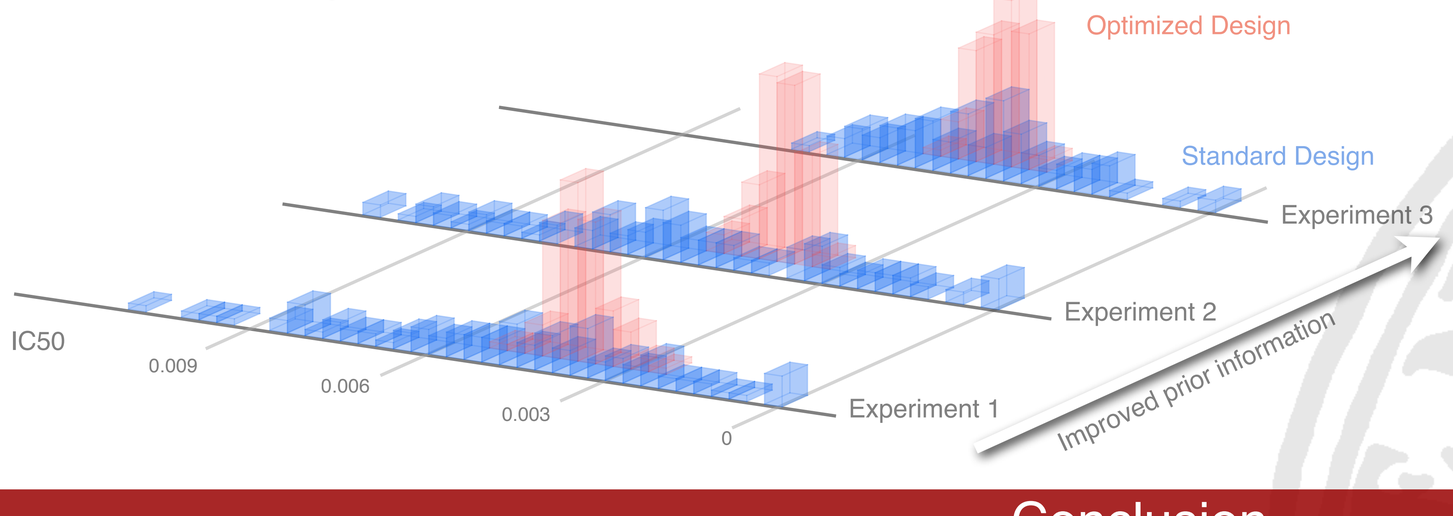


Step3: Inspect the design and modify if necessary



Benefit of Optimal Design in a Preclinical Study

To illustrate the benefit of optimizing experimental designs using **POPED** lite, we used the best model to simulate 100 plausible datasets for the standard and the optimized experimental designs. For each dataset we estimated the parameters. Data in the histograms indicate improved parameter precision for the optimized design compared to the standard design.



Summary of Features

D / Ds / ED / EDs optimal design

Precoded 1,2,3 compartment PK model with linear and nonlinear elimination.

Oral, iv-bolus, iv-infusion multiple doses.

Fully flexible PD model provided either by a closed form or by an ordinary differential equation, with or without effect compartment.

Parallelized Fischer Information Matrix computation.

Flexible yet easy to specify experimental constraints, e.g.,

- timeframe of observations / dose events
- time interval between observations
- total amount of the compound available

Conclusion

The study shows that the optimization of both sampling time and dosing scheme, especially the latter, can increase the accuracy of the estimation of the potency of the drug as well as other drug related parameters. Also, it is important to identify the practical experimental design constraints, such as the possible time frame of observations, the possible time interval between observations, or the total amount of the compound available, that can influence the optimal experimental design, and incorporate these constraints into the design optimization algorithm.

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