PODE 2014
Population Optimum Design of Experiments: Workshop
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A tale of introducing optimal design to preclinical experimentalists

Yasunori Aoki[12], Monika Sundqvist[3], Peter Gennemark[3] and Andrew C. Hooker[1]

1 Pharmacometrics Research Group Uppsala University, Sweden
2 Department of Mathematics Uppsala University, Sweden
3 CVMD iMed DMPK AstraZeneca R&D Mölndal, Sweden

To make the optimization of the preclinical experimental design a standard workflow in the compound selection studies, we have worked closely with preclinical experimentalists at AstraZeneca R&D in Mölndal. As a result, we have created a standalone software PopED lite to make optimal design accessible to the preclinical experimentalists. In this talk, we will share the challenges we have faced on introducing the idea of optimal design to actual experimentalists and explain how we have designed the software to overcome these challenges.

To design PopED lite, we have first assessed the necessary flexibility of the software for the use in preclinical experiment so that the software can be as simple as possible. Also we have investigated the level of accuracy needed for the practical use so that the software can suggest an optimal experimental design as fast as possible. Then, lastly, we have considered the background technical knowledge of a typical preclinical experimentalists so that the interface of the software is intuitive to users.

In order to demonstrate the use of PopED lite, we have conducted two retrospective analyses of already ran preclinical experiments, and demonstrated that by employing PopED lite, we could have reduced the use of animals, duration of experiment, and compound used while increasing the estimation accuracy of the compound potency. As a result, the preclinical experimentalists are more comfortable with the use of optimal design and now PopED lite is used to design preclinical experiments and has been contributing the accurate understanding of the compounds during the compound selection studies.

PopED lite is available from the following URLs:

https://itunes.apple.com/us/app/poped-lite/id836277613?mt=12
http://www.bluetree.me/PopED_lite.html

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Experiment Design Based on Bayes Risk and Weighted Bayes Risk with Application to Pharmacokinetic Systems

David S. Bayard[*1], Roger Jelliffe[*2], and Michael Neely[*3]

Laboratory of Applied Pharmacokinetics
Children's Hospital of Los Angeles (CHLA)
Los Angeles, California

This report investigates an experimental design method, MMopt, which minimizes an overbound on the Bayes Risk. MMopt provides an advantageous alternative to D-optimality and other criteria based on the asymptotic Fisher Information matrix. Advantages of MMopt are: (1) it avoids the circular reasoning associated with having to know a patient's true parameters in order to design an experiment; (2) it avoids using an asymptotic information measure for an experiment design that only places a small number of samples; (3) it is optimized using time-response data only. This last property is very powerful, permitting optimization with or without a specific structural model.

A new result is presented that introduces weighting into the Bayes risk cost. The weighted form of MMopt is especially useful for PK problems, where the experiment design can be tailored to be most informative about specific metrics such as AUC, maximal concentration, or what best future dose to give. A theoretical result shows that the weighted MMopt preserves the overbound of [1]. This is important because it allows bound-optimal designs to be systematically calculated as in the unweighted MMopt case. MMopt appears superior to ED optimal design, which also incorporates a Bayesian prior, when applied to several problems of practical interest.

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*[1,2] Scientific consultants to the CHLA Laboratory of Applied Pharmacokinetics
*[3] Director of the CHLA Laboratory of Applied Pharmacokinetics

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Influence of the size of the cohorts in adaptive design for nonlinear mixed effect models: an evaluation by simulation for a pharmacokinetic (PK) and pharmacodynamic (PD) model in oncology.

Giulia Lestini, Cyrielle Dumont, France Mentré

IAME, UMR 1137, INSERM, University Paris Diderot, Paris, France

Objectives: Optimal design in population PKPD is based on prior information on the models and parameters. Adaptive designs [1, 2] are a promising alternative to local or robust designs [3]. Two-stage designs are easier to implement than fully adaptive designs and can be as efficient [4]. Here, we compared by simulation several one-stage designs and two-, three- and five-stage adaptive designs.

Methods: We used the PKPD model of a drug in development in oncology [5] and we assumed that the model is known. We defined two sets of population parameters: wrong "prior" parameters Ψ^0[6], and "true" parameters, Ψ^*.We evaluated several designs of N=50 patients by clinical trial simulation.

We first defined two 'reference' one-stage designs ξ^0 and ξ^*optimized with Ψ^0 and Ψ^*, as the worst and best designs, respectively. Two-stage designs are composed of a first cohort of N_1 patients with design ξ^0 and a second cohort of N_2 patients with design ξ_2, ξ_2 being optimized using parameter estimates from data collected after first stage. Various two-stage designs with different cohort sizes at each stage (N_1+N_2=50) were studied. We finally compared one two-stage adaptive design with 2 three- and 1 five-stage adaptive designs, with N_1=10 patients in the first cohort.

Design optimization was performed using determinant of the Fisher Information Matrix (FIM) within PFIM 4.0 [7]. For the adaptive designs, prior information obtained after each stage was incorporated in the evaluation of FIM [2]. We simulated 100 datasets for each scenario using true parameters Ψ^*. Parameters were then estimated using the SAEM algorithm in MONOLIX 4.3. Relative Bias (RB) and Relative Root Mean Square Error (RRMSE) were used to compare the various designs.

Results: Estimation results with two-stage designs were close to those with the optimal design ξ^* and much better than those with the prior design ξ^0. The balanced two-stage design ($N_1= N_2=25$) performed better than unbalanced two-stage designs. The three- and five-stage designs were better than the two-stage adaptive design with a small first cohort ($N_1=10$), but not better than the balanced two-stage design.

Conclusions: Two-stage designs improve the design after the first cohort and are therefore useful when prior information on parameters is not reliable. In this study we found that the balanced two-stage design was the best. In case of small first cohort, more adaptive steps are needed, but these designs are more complex to implement.

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Optimal sampling times for pharmacokinetic modelling of a cocktail of phenotyping drugs

Thu Thuy Nguyen[1], Henri Bénech[2], Marcel Delaforge[2], Alain Pruvost[2], France Mentré[3], Natacha Lenuzza[1]

[1]CEA, LIST, Data Analysis and Systems Intelligence Laboratory, Gif-sur-Yvette, France;
[2]CEA, DSV, iBiTecS, Gif-sur-Yvette, France;
[3]IAME, UMR 1137, INSERM - University Paris Diderot, Paris, France

"Cocktail" of drugs is of high interest to determine enzyme activity responsible for drug metabolism and pharmacokinetics. Phenotyping indexes can be derived from a few samples using nonlinear mixed effect models (NLMEM) for analyzing drug concentrations and maximum a posteriori estimation (MAP) of individual parameters. We proposed an informative design common to two molecules for a phenotyping study: midazolam (probe for CYP3A activity) and digoxin (P-glycoprotein).

Using data of a previous study, NLMEM for midazolam, its 1-OH-metabolite and digoxin were developed in software MONOLIX4.2. Based on these models, we proposed a common design using a compound optimality criterion which is a weighted sum of log determinants of population Fisher information matrix (FIM) for each compound. The resulting design was evaluated for MAP and predicted shrinkages were reported, based on Bayesian FIM, using R function PFIM 4.0. Finally, sampling windows were computed around the optimal times, satisfying an expected joint loss of efficacy (evaluated by Monte-Carlo simulation) < 5%.

The common design was composed of six samples (0.25, 1, 2.5, 5, 12, 48h post-administration) instead of ten samples if considering separately each molecule. Predicted relative standard errors of derived phenotyping indexes were < 30%, with shrinkages < 50%. The sampling windows provided more flexibility while maintaining 95%-efficacy, compared to the optimal design.

By combining NLMEM, compound design and sampling windows based on FIM, we were able to determine sparse samples allowing correct estimation of parameters for three compounds. This approach can be extended to efficiently design studies with cocktails including more drugs.

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FIM Based Power Calculations for NLMEMs

Sebastian Ueckert

University of Uppsala, Sweden

Estimating the power of a future clinical study is a common problem in the drug development process. Within the framework of model based drug development this problem is solved through Monte-Carlo (MC) studies where numerous replicates of the trial are simulated and subsequently analysed. This process can be very time consuming due to the high number of replicates required to obtain a stable power estimate. Non-linear mixed effect models which are frequently used for the analysis of clinical trial data are especially problematic as they can have runtimes of several hours.

An alternative to time consuming MC studies are power calculations based on the Fisher information matrix. In this work three different information matrix based methods for power calculation were considered:

1. Wald statistic based power using a linear H_0 hypothesis
2. Wald statistic based power using a non-linear H_0 hypothesis
3. Parametric power estimation

All three methods were used to calculate the power to detect a drug effect in a hypothetical Alzheimer's trial based on a disease progression model from the literature. The obtained power versus samples size curves were compared to power values from a MC study.

The Wald statistic based power using a non-linear hypothesis as well as the parametric power estimation method were in good agreement with MC based power though slightly negatively biased. The Wald statistic using the linear the hypothesis, however, largely over-predicted the empirical power.

In conclusion, non-linear Wald and parametric power estimation are attractive alternatives to computationally intensive MC power studies.

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