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Optimal designs for dose response curves with common parameters

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A common problem in Phase II clinical trials is the estimation of dose-response curves. Typically the effect of the dose levels is described by parametric regression models. When treatment groups differ not only in terms of dose, but also in other aspects of the administration (e.g. frequency), it can make sense to assume that the same dose-response model holds overall, but some dose-response model parameters are shared while others are not shared between the different groups. In this talk we present results from optimal design theory for regression models with common parameters. We derive upper bounds on the number of support points of admissible designs. Explicit expressions for D-optimal designs are derived for specific situations. The results are illustrated by an application.

Informative study designs, where modelling and simulation based design features make a trial more informative than a comparable standard design

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Drug development should extract maximum information from experimental protocols with minimized exposure of patients to invasive procedures and potentially harmful drug exposure and minimized investment of time and money. Aspects of study design are explored illustrating how information can be extracted more efficiently by investigating a range of exposures within individuals rather than relying on cross-sectional analyses, either by following individual patient responses as their drug concentrations decline or by within-individual dose escalation. The designs are evaluated considering the uncertainty in the parameters to assess robustness of these approaches.

Using Hamiltonian Monte-Carlo to design longitudinal count studies accounting for parameter and model uncertainties

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Nonlinear mixed effect models (NLMEMs) are widely used for the analysis of longitudinal data. To design these studies, optimal designs based on the expected Fisher information matrix (FIM) can be used. A method evaluating the FIM, without any linearization, based on Monte-Carlo Hamiltonian Monte-Carlo (MC-HMC) has been proposed and implemented in the R package MIXFIM [1] using Stan [2], which efficiently draws HMC samples and calculates partial derivatives of the log-likelihood. This approach, however, requires a priori knowledge of models and parameters, which leads to designs that are locally optimal. The objective of this work was to extend this MC-HMC-based method to evaluate the FIM in NLMEMs accounting for uncertainty in parameters and in models, and to apply the proposed approach to repeated count data.

When introducing uncertainty in the population parameters, we evaluated the robust FIM as the expectation of the FIM computed by MC-HMC for the population parameters. Then, the compound D-optimality criterion [3, 4] was used to find a common CD-optimal design for several candidate models. A compound DE-criterion was used to find the CDE-optimal design which was robust with respect to both parameters and model. These methods were applied in a longitudinal Poisson count model where the event rate parameter is a function of the dose level. We assumed a log-normal a priori distribution characterizing the uncertainty in the population parameter values as well as several candidate models describing the relationship between the logarithm of the event rate parameter and the dose level. We performed combinatorial optimization of two doses. Assuming uncertainty in parameters led to different optimal designs, and misspecification of models led to designs with low efficiencies. The CD- or CDE-optimal designs provided a good compromise for different candidate models.

In conclusion, MC-HMC is a relevant approach allowing for the first optimization of designs for repeated discrete data accounting for uncertainty in parameters and in candidate models.

References:

[1] Riviére, M.K., Ueckert, S., and Mentré, F. An MCMC method for the evaluation of Fisher information matrix for non-linear mixed effect models. *Biostatistics*, 2016; 17 (4), 737-750.

[2] Stan Development Team. RStan: the R interface to stan, version 2.12.0, 2016. `http://mcstan.org/`

[3] Atkinson, A.C., DT-optimum designs for model discrimination and parameter estimation. *Journal of Statistical Planning and Inference*, 2008.

[4] Nguyen, T. T., Benech, H., Delaforge, M., and Lenuzza, N. Design optimisation for pharmacokinetic modeling of a cocktail of phenotyping drugs. *Pharmaceutical Statistics*, 2016; 15 (2), 165-177.

Sparse sampling design for characterizing individual PK of recombinant factor VIII fusion protein (rFVIIIFc) in prophylactic treatment of Hemophilia A

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Objectives: To determine sparse sampling times for estimating individual rFVIIIFc maximum a priori (MAP) Bayesian estimates in children ($<$12yr) and adults/adolescents ($\geq$12yr) and to evaluate the effectiveness of the recommended times to estimate individual pharmacokinetic (PK) parameters.

Methods: Fisher information matrix (FIM) for Bayesian MAP estimator [1] was implemented in PopDes, determinant of the FIM was optimized to derive optimal sampling times, assuming a dose of 50 IU/kg and 10 minutes intravenous infusion. Previously developed population PK model provided prior information. Robust three and two time points were proposed to estimate individual PK parameters based on Bayesian methodology and their effectiveness was investigated using simulations. Plasma FVIII activities of 1000 random individuals were simulated using the population PK model for different designs, individual MAP Bayesian estimates and their relative errors were determined.

Results: Optimal three sampling times for children and adolescent/adults were identified. Despite informative prior on volume, an earlier time-point at 0.5h was explored for the robust, practical sampling design to better estimate individual volume. Robust and practical three and two time points designs were identified for children and adults/adolescents with efficiencies relative to the optimal time points of approximately 91% and 83% for three and two time points respectively. Due to possible loss of information to data below lower limit of quantification at later time points, alternative three and two time points were derived; (0.5, 24, 48)h and (0.5, 48)h for children and (0.5, 48, 72)h and (0.5, 72)h for adults/adolescents. Relative to the optimal time points, the efficiencies of these designs were approximately between 70% and 95%. Simulation results showed adequate MAP Bayesian parameter estimation by both robust designs; mostly with relative errors within 25 to 30%.

Conclusion: Robust three and two sampling times for estimation of individual MAP Bayesian estimates were successfully derived and the simulations indicated that these allowed adequate estimation of individual PK of rFVIIIFc which could then subsequently be utilized for dose individualization.

References:

[1] Hennig S., Nyberg J., Fanta S, Backman J.T., Hoppu K., Hooker A.C., Karlsson M.O. Application of the optimal design approach to improve a pretransplant drug dose finding design for ciclosporin. *The Journal of Clinical Pharmacology*, 52: 347-60 (2012)

Getting started with Optimal Design for NLME models

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With the growing need of improving the way experimental designs are elaborated to allow for a precise parameter estimation using the minimal number of individuals and sampling points, the interest on model-based optimal design (OD) as a tool to evaluate and optimise experiments beforehand is greatly increasing. Currently, there are several tools available for OD applied to NLME. However, given the lack of comprehensive tutorials and still scarce literature, pharmacometricians frequently have difficulties to select the most suitable tool and algorithm according to their design scenario, tackle warnings and errors, and critically judge and present the results. The aim of this talk is to present the challenges that newbies face when getting started into the field of optimal design.

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Exposure-response modeling for dose selection under model uncertainty: Extending the MCP-Mod approach

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Poor dose-regimen selection resulting from insufficient knowledge of the dose-exposure-response relationship remains one of the key challenges in clinical drug development, believed to be associated with the high attrition rates observed in confirmatory trials. Different methods have been proposed to improve on the conventional, inefficient paradigm of pairwise testing of active doses versus placebo, among them MCPMod. This approach has the appealing feature of combining well-established aspects of hypothesis testing and modeling, implementing dose-response estimation and dose selection under model uncertainty. MCPMod has recently received a positive Qualification Opinion from CHMP/EMA, as well as a Fit-for-Purpose denomination from the U.S. FDA. The original formulation and extensions to date of MCPMod have been restricted to dose-response modeling and testing of dose-response signal, under a wide range of response types (e.g., continuous, binary, time to event, etc.). This talk describes an extension of the MCPMod methodology to exposure-response modeling (and signal testing) under model uncertainty. Examples and simulations will be presented to illustrate the use of the proposed approach, using the current implementation of MCPMod in the DoseFinding R package.

Joint work with Yevgen Tymofyeyev and Alberto Russo, Janssen R&D

Optimal designs for the prediction of individual parameters in multiple group random coefficient regression models

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Optimal designs for the prediction of individual parameters in multiple group Random Coefficient Regression (RCR) models are very popular in many fields of statistical application; especially in biosciences. In these models observational units (individuals) are assumed to come from the same population with an unknown population mean and differ from each other by individual random parameters. Besides the estimation of the population mean parameter, the prediction of the individual response is often of prior interest. In the particular case of multiple group RCR models individuals in different groups get different kinds of treatment. If group sizes are fixed and the unknown mean parameters may differ from group to group, statistical analysis can be performed in each group separately [1]. This talk presents analytical results for optimal group sizes for the prediction of the individual parameters in multi group RCR models with a common population mean for all individuals across all groups.

References:

[1] Prus, M. *Optimal Designs for the Prediction in Hierarchical Random Coefficient Regression Models.* Ph.D. thesis, Otto-von-Guericke University Magdeburg (2015).

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Implementing optimal designs for dose-response studies through adaptive randomization for a small population group

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In dose-response studies with censored time-to-event outcomes, D-optimal designs depend on the true model parameters and on the amount of censoring in the model. In practice, such designs can be implemented adaptively, by performing dose assignments according to updated knowledge of the dose-response curve at interim analysis. It is also essential that treatment allocation involves randomization to mitigate various experimental biases and enable valid statistical inference at the end of the trial.

In this work we perform a comparison of several adaptive randomization procedures that can be used for implementing D-optimal designs for dose-response studies with time-to-event outcomes with small to moderate sample sizes. The operating characteristics of randomization procedures involve measures of treatment allocation balance, randomness of treatment assignments, variations in the allocation ratio, and statistical characteristics such as type I error rate, power, and estimation efficiency. For a small sample size, the commonly used completely randomized design (CRD) results in higher variance of model parameters' estimation and less power compared to the procedures targeting optimal allocation proportions. The results of the current work should help clinical investigators select an appropriate randomization procedure for their dose-response study. We also present a web-based R shiny application that can be used to reproduce all results in this presentation and perform additional simulations for user-defined experimental scenarios.

Keywords: D-optimal design, Dose-response study, Randomization, Time-to-event outcomes, Unequal allocation.

Robust designs for longitudinal trials with binary data taking into account model uncertainty

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Background/Objectives: Nonlinear mixed effect models (NLMEMs) are used in model-based drug development to analyze all longitudinal data obtained during clinical trials. Finding good design for these studies is important to get precise results and/or good power especially in case of sparse sampling. To design these studies, the expected Fisher Information Matrix (FIM) can be used. A method evaluating the FIM, without any linearization, based on Monte-Carlo and Hamiltonian Monte-Carlo (MC/HMC), has been proposed and implemented in the R package MIXFIM [1], which performs well with both continuous and discrete data. Nevertheless, this approach requires a priori knowledge of the model. We aim to propose and illustrate a robust approach based on MC/HMC to incorporate model uncertainty when designing a longitudinal study with repeated binary outcomes including two treatment groups.

Methods: To determine informative sampling times for a given model, different optimality criteria based on the FIM evaluated by MC/HMC can be computed, according to different purposes: the D-optimality to optimize the precision of the whole set of population parameters, the DS-optimality to accommodate situations in which only a subset of the model parameters is of interest (e.g. covariate effects), and the DDS-optimality to find a compromise between the D- and DS-optimality [2]. Then, uncertainty in model is taken into account using the compound D-, DS- and DDS-optimality to find informative designs which are robust across a set of candidate models. These methods are applied to design a longitudinal study in two treatment groups of 50 individuals. We consider four candidate NLMEMs for binary responses over time. Combinatorial optimization is performed to determine four informative sampling times, common to all these models. Using the expected FIM, we also predict the number of subjects needed to detect a significant treatment effect for each model with a power of 80%. The performance of the compound DDS-optimal design is evaluated by Clinical Trial Simulations (CTS) in terms of precision of parameter estimation and power of test to detect a treatment effect.

Results: Assuming uncertainty in candidate models lead to different optimal designs, and misspecification of models lead to designs with low efficiencies. The compound criteria provide robust CD-, CDS- and CDDS-optimal designs which are efficient across the four candidate models. In addition, the CDDS-optimal design allows a compromise between the overall precision of estimation and the power of test. The estimation error and the power predicted using the expected FIM for the finally proposed design are overall close to the values obtained by CTS.

Conclusions: The proposed design strategy based on MC/HMC and compound optimality theory, is a relevant approach which can be used to efficiently design longitudinal studies accounting for model uncertainty.

References:

[1] Riviere M-K, Ueckert S, Mentré F. An MCMC method for the evaluation of the Fisher information matrix for non-linear mixed effect models. *Biostatistics*. 2016; 17:73750.

[2] Atkinson A. C., Bogacka B. Compound D- and Ds-Optimum Designs for Determining the Order of a Chemical Reaction. *Technometrics*. 1997; 39:34756.