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Cost constrained optimal designs for regression models with random parameters

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I describe various optimization problems related to the design of experiments for regression models with random parameters, aka mixed effect models and population models. In the terms of the latter two different goals can be pursuit: estimation of population parameters and individual parameters. Respectively we have to face two types of optimality criteria and cost constraints. Additional strata appear if one would observe that the following two experimental situations occur in practice: either repeated observations are admissible for a given experimental unit (object or subject), or not. Clinical studies with multiple sites with slightly different treatment outcomes (treatment-by-cite interaction) is an example when repeated and independent observation are possible - a few subjects can on each treatment arm. PK studies may serve as an example when repeated observations cannot be performed - only one observation at the given moment can be performed on a subject. All these caveats lead to the different design problems that I try to link together.

Model based adaptive optimal designs of adult to children bridging studies using an FDA proposed stopping criteria.

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Abstract: In this work we apply the FDA proposed precision criteria necessary for pediatric pharmacokinetic studies (Wang et. al., 2012) as a stopping criteria for a model based adaptive optimal design (MBAOD) of an adult to children pharmacokinetic bridging study. We demonstrate the power of the MBAOD compared to both traditional designs as well as non-adaptive optimal designs.

Design and analysis of in-vitro pharmacokinetic experiments

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In many pharmacokinetic experiments, the main goal is to identify enzymes that are related to the metabolic process of a substrate of interest. Since most of the enzymes that are involved in drug metabolism are located in the liver, human liver microsomes (HLMs) are used in these in vitro experiments. Experimental runs are conducted for each HLM at different levels of substrate concentration and the response, the initial rate of reaction, is measured from each experimental run. The relationship between such a response and the substrate concentration is usually nonlinear and so it is assessed from the size of the nonlinear regression parameters. However, the use of different HLMs requires additional random effects and there might also be covariate information on these HLMs. A further complication is uncertainty about the error structure of the resulting nonlinear mixed model. Methods for obtaining optimal designs for such models will be described. The resulting designs will be compared with the larger designs used in current practice. It will be shown that considerable savings in experimental time and effort are possible. Practical issues around the design and analysis will be discussed, along with suggestions of how the methods are best implemented.

Optimal design and parameter estimation for population PK/PD models

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In this presentation we discuss methods of model-based optimal experimental design that are used in population pharmacokinetic/pharmacodynamic studies and focus on links between various parameter estimation methods for nonlinear mixed effects models and various options for approximation of the information matrix in optimal design algorithms.

Evaluation of the Fisher information matrix in nonlinear mixed effect models using Monte Carlo Markov Chains

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For the analysis of longitudinal data, and especially in the field of pharmacometrics, nonlinear mixed effect models (NLMEM) are used to estimate population parameters and the interindividual variability. To design these studies, optimal design based on the expected Fisher information matrix (FIM) can be used instead of performing time-consuming clinical trials simulations. Until recently, the FIM in NLMEM was mostly evaluated with first-order linearization (FO). We propose an approach to evaluate the exact FIM using Monte Carlo (MC) approximation and Markov Chains Monte Carlo (MCMC). Our approach is applicable to continuous as well as discrete data and was implemented in R using the probabilistic programming language STAN. This language enables to efficiently draw MCMC samples and to calculate the partial derivatives of the conditional log-likelihood directly from the model. The method requires several minutes for a FIM evaluation but yields an asymptotically exact FIM. Furthermore, computation time remains similar even for complex models with many parameters. We compare our approach to clinical trials simulation for various continuous and discrete examples.

Computation of the Fisher information matrix for discrete non-linear mixed effect models

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Despite an increasing use of optimal design methodology for non-linear mixed effect models (NLMEMs) during the clinical drug development process (Mentré et al., 2013), examples involving discrete data NLMEMs remain scarce (Ernest et al., 2014). One reason are the limitations of existing approaches to calculate the Fisher information matrix (FIM) which are either model dependent and based on linearization (Ogungbenro and Aarons, 2011) or computationally very expensive (Nyberg et al., 2009). The main computational challenges in the computation of the FIM for discrete NLMEMs evolve around the calculation of two integrals. First the integral required to calculate the expectation over the data and second the integral of the likelihood over the distribution of the random effects. In this presentation Monte-Carlo (MC), Latin-Hypercube (LH) and Quasi-Random (QR) sampling for the calculation of the first as well as adaptive Gaussian quadrature (AGQ) and QR sampling for the calculation of the second integral are proposed. The resulting methods are compared for a number of discrete data models and evaluated in the context of model based adaptive optimal design.

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Incorporating pharmacokinetic information in phase I studies in small populations

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Objectives: To review and extend existing methods which take into account PK measurements in sequential adaptive designs for early dose-finding studies in small populations, and to evaluate the impact of PK measurements on the selection of the maximum tolerated dose (MTD).

Methods: This work is set in the context of phase I dose-finding studies in oncology, where the objective is to determine the MTD while limiting the number of patients exposed to high toxicity. We assume toxicity to be related to a PK measure of exposure, and consider 6 possible dose levels. Three Bayesian phase I methods from the literature were modified and compared to the standard continual reassessment method (CRM) through simulations. In these methods PK measurement, more precisely the AUC, is present as covariate for a link function of probability of toxicity (Piantadosi and Liu (1996), Whitehead et al. (2007)) and/or as dependent variable in linear regression versus dose (Patterson et al. (1999), Whitehead et al. (2007)). We simulated trials based on a model for the TGF- inhibitor LY2157299 in patients with glioma (Gueorguieva et al., 2014). The PK model was reduced to a one-compartment model with first-order absorption as in Lestini et al. (2014) in order to achieve a close solution for the probability of toxicity. Toxicity was assumed to occur when the value of a function of AUC was above a given threshold, either in the presence or without inter-individual variability (IIV). For each scenario, we simulated 1000 trials with 30, 36 and 42 patients.

Results: Methods which incorporate PK measurements had good performance when informative prior knowledge was available in term of Bayesian prior distribution on parameters. On the other hand, keeping fixed the priors information, methods that included PK values as covariate were less flexible and lead to trials with more toxicities than the same trials with CRM.

Conclusion: Incorporating PK values as covariate did not alter the efficiency of estimation of MTD when the prior was well specified. The next step will be to assess the impact on the estimation of the dose-concentration-toxicity curve for the different approaches and to explore the introduction of fully model-based PK/PD in dose allocation rules.

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Designs for generalized linear models with random block effects

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For an experiment measuring independent discrete responses, a generalized linear model, such as the logistic or log-linear, is typically used to analyse the data. In blocked experiments, where observations from the same block are potentially correlated, it may be appropriate to include random effects in the predictor, thus producing a generalized linear mixed model. Selecting optimal designs for such models is complicated by the fact that the Fisher information matrix, on which most optimality criteria are based, is computationally expensive to evaluate. In addition, the dependence of the information matrix on the unknown values of the parameters must be overcome by, for example, use of a pseudo-Bayesian approach.

For the first time, we evaluate the efficiency, for estimating conditional models, of optimal designs from closed-form approximations to the information matrix, derived from marginal quasi-likelihood and generalized estimating equations. It is found that, for binary-response models, naive application of these approximations may result in inefficient designs. However, a simple correction for the marginal attenuation of parameters yields much improved designs when the intra-block dependence is moderate. For stronger intra-block dependence, our adjusted marginal modelling approximations are sometimes less effective. Here, more efficient designs may be obtained from a novel asymptotic approximation. The use of approximations from this suite reduces the computational burden of design search substantially, enabling straightforward selection of multi-factor designs.