

# Design and Analysis of Experiments 2012

Abstracts

## **Bayesian Design for Spatial Processes**

**Maria Adamou**

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**Collaborators/co-authors:** Sue Lewis, Sujit Sahu and Dave Woods

Spatial data are collected in many diverse application areas including studies in climatology, environmental and ecological science. Often, such data are used for both estimation of the statistical process based models and predictions of the processes at unobserved spatial locations. These models are typically described by a spatial correlation structure that may also depend upon unknown parameters. Hence, the design of the sampling plan influences the quality of the model fit and subsequent analysis and prediction.

We construct optimal designs for spatial data through the best choice of sampling locations in the geographical region of interest. The aims of our spatial experiments are accurate estimation of the model to describe the response and precise predictions of the response at unobserved locations. A decision theoretic design problem is formulated and Bayesian optimality criteria are derived from loss functions that are chosen according to these aims. The resulting designs are illustrated through a number of examples. Although the design problem is motivated by spatial applications, the design criteria can also be applied to higher dimensional models, e.g. with covariates, or to more general multi-variable prediction problems.

## **Randomness and Biased-Coin Designs**

**Anthony C. Atkinson**

Department of Statistics, London School of Economics

In 1972 Efron introduced a biased-coin design for the sequential allocation of one of two treatments when it is not known how many patients are required. One goal of the design is that it should not be too far from balance whatever the value of  $n$  at which the trial is stopped. The other is that the allocation should be sufficiently random that selection bias is small, that is there is a low probability of correctly guessing the next allocation. These two requirements are in conflict: a deterministic rule can provide a maximum imbalance of one but at the cost of a probability of one of guessing the next allocation whenever  $n$  is odd; with random allocation, selection bias is zero but the design may become appreciably unbalanced.

In Efron's rule the probability of allocation of the less-allocated treatment is  $p = 2/3$ . Although other values of  $p$  can be used, the rule is such that  $p$  does not depend on the value of the imbalance in allocations. Since Efron's proposal several other rules have been suggested which force greater balance by having  $p$  increase with imbalance.

The purpose of the talk is to provide a framework for the comparison of these rules in terms of selection bias and of ‘loss’, which indicates the increase in variance of treatment comparisons due to imbalance. Analysis of these quantities as functions of  $n$  shows that the rules fall into three distinct categories: those for which the loss decreases with  $n$ , those for which it is stable and those for which it increases. Plots of loss against selection bias indicate that some rules are inadmissible, in that they have higher loss and higher bias than others for all  $n$ . But the main argument of the talk is in favour of rules in which loss increases with  $n$ , since, at the same time, bias decreases. Larger imbalances with large  $n$  have a small effect on the efficiency of estimation and on the power for tests about treatment effects. But, for small  $n$ , balance is paramount.

### **Composite Gaussian Process Model for Emulating Expensive Functions**

**Shan Ba**

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**Collaborators/co-authors:** V. Roshan Joseph

A new type of non-stationary Gaussian process model is developed for approximating computationally expensive functions. The new model is a composite of two Gaussian processes, where the first one captures the smooth global trend and the second one models local details. The new predictor also incorporates a flexible variance model, which makes it more capable of approximating surfaces with varying volatility. Compared to the commonly used stationary Gaussian process model, the new predictor is numerically more stable and can more accurately approximate complex surfaces when the experimental design is sparse. In addition, the new model can also improve the prediction intervals by quantifying the change of local variability associated with the response. Advantages of the new predictor are demonstrated using several examples.

### **Designs for Dose-escalation Trials**

**R. A. Bailey**

Queen Mary, University of London

When new drugs are tried in humans for the first time, lower doses must be tried before higher ones so that the trial can be stopped early if the drug causes harm. One possibility is that one cohort of volunteers is exposed to the first dose; if there are no harmful side-effects then, one or two weeks later, a second cohort is exposed to the next dose, and so on. That simple-minded approach completely confounds doses with cohorts, so the more usual approach allocates a few volunteers to placebo in each cohort. In *Statistics in Medicine* in 2009 I proposed a new design which reduces the variance of estimators by up to a third if there are cohort effects, without compromising safety or using more volunteers. In this talk I shall report on further progress made, by others as well as me, since then.

## **On Optimal Designs for Nonlinear Models: a General and Efficient Algorithm**

**Stefanie Biedermann**

University of Southampton, UK

**Collaborators/co-authors:** Min Yang

Deriving optimal design for nonlinear models is challenging in general. Although some recent developments allow us to focus on a simple subclass of designs for many problems, deriving a specific optimal design mainly depends on algorithmic approaches. There is need of a general and efficient algorithm which is more broadly applicable than the current state of the art methods. We present a new algorithm that can be used to find optimal designs with respect to a broad class of optimality criteria, when the model parameters or functions thereof are of interest, and for both locally optimal and sequential design strategies. We prove convergence to the desired optimal design, and show that the new algorithm is highly efficient.

## **Optimum Designs for Parameter Estimation and Model Discrimination in Enzyme Inhibition Studies**

**Barbara Bogacka**

Queen Mary, University of London

**Collaborators/co-authors:** A. C. Atkinson, P. Johnson, M. Patan and K. Youdim

We find closed-form expressions for the D-optimum designs for three- and four-parameter nonlinear models arising in kinetic models for enzyme inhibition. Experimental results from a standard design with 120 trials and a D-optimum design with 21 trials give parameter estimates that are in close agreement. The estimated standard errors of these parameter estimates confirm our theoretical results on efficiency and thus on the serious savings that can be made by the use of D-optimum designs.

A general model for enzyme kinetics with inhibition, the mixed inhibition model, simplifies to the non-competitive inhibition model when two of the parameters are equal. We reparamaterise the model and provide designs for investigating the equality of parameters, which corresponds to a scalar parameter  $\delta$  being zero. For linear models T-optimum designs for discriminating between models in which  $\delta$  is, and is not, equal to zero are identical to designs in which the estimate of  $\delta$  has minimum variance. We show that this equality does not hold for our nonlinear model, except as  $\delta$  approaches zero. We provide optimum discriminating designs for a series of parameter values.

## **Digital Experience Optimization: A New Frontier of Application of the Design of Experiments**

**Vladimir Brayman**

Webtrends

Digital experience optimization emerged recently as an important area of applied research. Availability of large amount of data that describes Web users' behavior on the one hand and never-ending

quest for better user experience and increased ROI on the other, have led to the development of systems that allow on-line vendors conduct automated testing of digital content. The results of the experiments are then analyzed and conclusions are drawn which content works best for particular audience segments. The on-line experimentation presents its own challenges. Among them is the demand for fractional factorial designs for a wide range of factor-level combinations, ability to interpret the results easily by non-statisticians, and a facility for estimating test duration. In this talk we present the results of the research done at Webtrends that led to the development of a state-of-the-art digital experience testing platform.

### **Experimental Designs for Different Approaches of Simultaneous Equations**

**Victor M. Casero-Alonso**

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**Co-author:** Jesus Lopez-Fidalgo

Models with simultaneous equations are considered. These models are widely used in experimental economics and business, among many other fields. In particular, a model with two equations is considered in this work. One of the explanatory variables (exogenous) of the first equation is the response variable (endogenous) of the second equation. In the second equation there is a controllable variable, which is being designed. If the second equation is plugged into the first one the designable variable is now in both equations. These are two different models producing different maximum likelihood estimators and therefore information matrices and optimal designs. Optimal designs for both approaches are computed and compared, both in a discrete and a continuous design space. The different cases of completely known correlation and a correlation dependent of estimable coefficients are considered and compared. A sensitivity analysis is performed in all cases to have an idea of the risk in choosing wrong nominal values of the parameters.

### **Construction of Search Designs from Orthogonal Arrays**

**Kashinath Chatterjee**

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**Collaborators/co-authors:** P. Angelopoulos and C. Koukouvinos

Search designs is an important class of experimental designs that allow the identifying of the true model, consisting of a set of factorial effects, among many. Most of the work in this field has been made in the cases where there are at most one or two two-factor interaction effects considered non-negligible. This paper focuses on model identification through the use of search linear models containing, apart from the general mean and the main effects, up to five non-negligible two-factor interaction effects. The new search designs are based exclusively on orthogonal arrays.

# **A Bayesian Response-based Adaptive Randomization Rule for a Phase II Clinical Trial of Targeted Therapy**

**Yiyi Chen**

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**Collaborators/co-authors:** Zunqiu Chen and Motomi Mori

Several FDA-approved agents may be used to effectively treat patients with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML). However, patients who fail to show response to one agent may respond well to some other agents. It is hypothesized that assigning drugs to ALL and AML patients based on the siRNA and Kinase inhibitor screen results will lead to better clinical outcomes. To assess the clinical utility of this drug selection strategy, we proposed a Bayesian response-based adaptive randomized phase II clinical trial design to evaluate whether assigning assay-matched treatment brings therapeutic benefits compared to assay-mismatched assignment of the treatment. The design assigns more patients to the treatment group with favorable interim results, making it better accepted by the patients and the physicians than a fixed ratio randomized trial. Five agents (Dasatinib, Sunitinib, Sorafenib, Nilotinib and Ponatinib) are evaluated in the trial with the following requirements: (1) all patients undergo a kinase inhibitor screen; (2) enrolled eligible patients must be sensitive to at least one of the five drugs under study, and; (3) eligible patients will be randomized to receive either an assay-matched or an assay-mismatched drug. The trial has two stages of randomization: the equal allocation stage (Stage I) and the adaptive allocation stage (Stage II). A hierarchical Bayesian model is used to estimate the objective response rate of each arm to the five drugs. We considered six potential adaptive randomization allocation rules for the Stage II and evaluated the performance of each through a simulation study for three scenarios. A modified allocation rule based on the optimal allocation ratio proposed by Rosenberger, Sallard, Ivanova, Harper and Ricks (RSIHR) has the most desirable performance than the other allocation rules in terms of the operating characteristics and the proportion of patients receiving the superior treatment.

## **Templates for Design Key Construction**

**Ching-Shui Cheng**

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**Collaborators/co-authors:** Pi-Wen Tsai

We present and justify some useful templates for implementing design key construction of factorial designs with simple block structures, in particular those for the construction of unblocked and blocked split-plot and strip-plot factorial designs. The traditional method of constructing such designs is to use some independent treatment factorial effects to partition the treatment combinations into blocks, rows, columns, etc. One advantage of the design key construction is that a set of independent generators and the constraints imposed by the structures of the experimental units are built in the template, which facilitates a systematic and simple construction of the design layout and eliminates the need to check some conditions for design eligibility when the traditional method is used.

## **Optimal Design of Experiments for Delayed Responses in Clinical Trials**

**Vladimir Dragalin**

Aptiv Solutions

The efficiency of optimal design of experiments when the primary endpoint is immediate is well documented. Often, however, in practice of clinical trials there will be a delay in the response of clinical interest. I will describe recent approaches that make use of short-term endpoints for interim adaptation. The focus of the definitive analysis is still the primary clinical endpoint and not the short-term endpoint. The short-term endpoints may be used just as necessary condition of potential treatment effect and can enhance the interim decision of dropping a treatment arm or changing the treatment allocation. The research questions are: what is the optimal number of measurements per patient and what are the optimal time intervals between these measurements. A major benefit of modeling relationships between early and late endpoints is that it makes for stronger interim assessments of long-term endpoints and therefore improves the efficiency of adaptive designs.

## **Sliced Full Factorial-Based Latin Hypercube Designs as a Framework for a Batch Sequential Design Algorithm**

**Weitao Duan**

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**Collaborators/co-authors:** Bruce E Ankenman

When fitting complex models, such as finite element or discrete event simulations, the experiment design should exhibit good properties of both projectivity and orthogonality. To reduce experimental effort, sequential design strategies allow experimenters to collect data only until some measure of prediction precision is reached. In this article, we present a batch sequential experiment design method that is based on sliced Full Factorial-Based Latin Hypercube Designs (FF-based LHD), which are an extension to the concept of sliced Orthogonal Array-Based Latin Hypercube Designs (OA-based LHD). At all stages of the sequential design, good univariate stratification is achieved. The structure of the FF-based LHD also tends to produce uniformity in higher dimensions especially at certain stages of the design. We show that the designs have good sampling and fitting qualities through both empirical studies and theoretical arguments.

## **Optimal Designs for Discriminating Between Functional Linear Models**

**Verity Fisher**

University of Southampton

**Collaborators/co-authors:** Dave Woods

Improvements in online measuring and monitoring have facilitated an increase in the number of observations that can be taken on each experimental unit in industrial and scientific experiments. Examples include biometry, chemistry, psychology and climatology. It can often be assumed that

the data for each run are generated by a smooth underlying function. We are interested in how changes to the levels of the controllable factors influence these functions. Often a semi-parametric model is assumed, with relatively simple polynomial models describing the treatment effects.

Methods are presented for the design of experiments with functional data when the aim is to discriminate between linear models for the treatment effect. We develop an extension of the  $T$ -optimality criterion to functional data for discriminating between two competing models. The methodology is demonstrated by an example from Tribology and assessed via simulation studies to calculate the sensitivity and specificity of the resulting analyses.

### **Adaptive Design for Non-Stationary Surfaces using Changes in Slope**

**Marian Frazier**

The Ohio State University

Computer experiments have been developed to study physical processes that are too costly, difficult, or dangerous to experiment with in the physical world. Complex computer code that simulates these physical experiments often results in an extremely long running time. Hence, the design at which to run the simulations must be chosen carefully and intelligently. An efficient design method that can investigate the response surface in a small number of samples is a must. With this in mind, sequential (adaptive) designs that allow users to focus their attentions on interesting areas of the response are a logical choice.

Historically, computer experiments included an assumption of stationarity, but Gramacy and Lee's Bayesian treed Gaussian process (TGP) has been shown to be effective at fitting non-stationary surfaces. We propose a sequential design method that is efficient at investigating non-stationary response surfaces. This method focuses on the search for areas with large changes in slope, with the idea that sudden changes in slope are an indication of non-stationary "breaks" in the response. While seeking out these boundary points, our method still results in an effective fit of the entire response surface. The merits of this method are exhibited in several examples, including comparisons to existing sequential design methods. With the understanding that this design method is specifically useful for non-stationary problems, all surface modeling will be done using the Bayesian TGP model.

### **On Sequential Designs Based on Maximum Likelihood Estimation**

**Fritjof Freise**

Otto-von-Guericke University Magdeburg

One of the problems optimal design in nonlinear models has to face is, that the information matrices and hence the resulting designs are depending on the actual value of the parameter. To tackle this problem a minimax or (pseudo-)Bayesian approach could be used.

Alternatively adaptive methods can be applied. In each step observations are taken, the parameter is estimated and new design points are determined using these estimates instead of the true value of

the parameter. Even though the dependency of estimates and design can be quite complicated, it is possible to rewrite the problem in some cases, such that methods from Stochastic Approximation can be applied.

Using this approach sequential procedures based on maximum likelihood estimation in logistic binary response models are investigated and the convergence of the sequence of estimators and designs are established.

### **Designs for Computer Experiments Constructed from Block-circulant Matrices**

**Stelios D. Georgiou**

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**Collaborators/co-authors:** Stella Stylianou

Computer simulations are usually needed to study a complex physical process. In this paper, we propose new procedures for constructing orthogonal or low-correlation block-circulant Latin hypercube designs. The basic concept of these methods is to use vectors with a constant periodic autocorrelation function to obtain suitable block-circulant Latin hypercube designs. A general procedure for constructing orthogonal Latin hypercube designs with favorable properties and allowing run sizes being different from a power of 2 (or a power of 2 plus 1), is presented here for the first time. In addition, an expansion of the method is given for constructing Latin hypercube designs with low correlation. This expansion is useful when orthogonal Latin hypercube designs do not exist. The properties of the generated designs are further investigated. Some examples of the new designs, as generated by the proposed procedures, are tabulated. In addition, a brief comparison with the designs that appear in the literature is given.

### **Randomization Procedures That Depend on the Covariates**

**Alessandra Giovagnoli**

University of Bologna

**Collaborators/co-authors:** Alessandro Baldi Antognini and Maroussa Zagoraiou

It goes without saying that in a clinical trial for comparing two or more treatments the role of prognostic factors may be crucial for drawing correct conclusions about treatment effects, so that covariates are of primary importance also at the design stage. In the last decade there has been a growing statistical interest in sequential allocation procedures adjusted for covariates. This presentation is a state-of-the-art one. The first part deals with recent results (Baldi Antognini and Zagoraiou, *Biometrika*, 2011) about balancing methods that go beyond the traditional minimization procedure. The second part focuses on covariate-adjusted response-adaptive (CARA) randomization methods which aim at skewing allocations towards the treatment that appears to be superior and presents the recently introduced Reinforced Doubly-adaptive Biased Coin Design (Baldi Antognini and Zagoraiou, *Annals of Statistics*, to appear).



## **Sequential Design for Constraint Satisfaction in Optimization Problems**

**Robert B. Gramacy**

The University of Chicago

**Collaborators/co-authors:** Herbie Lee, Stefan Wild, Genetha Gray and Sebastien Le Digabel

The expected improvement (EI) and variants are a popular sequential design heuristics for solving blackbox optimization problems. Although not generally regarded as superior for conventional optimizations—unless function evaluations are very expensive, or have many minima—it does have nice global convergence properties not enjoyed by most alternatives and remains one of a few viable options when the objective function evaluations can only be observed with noise. In this talk we discuss the far greater potential for statistical approaches to constrained blackbox optimization, a far more common and much harder engineering problem. We observe that modern nonparametric classification models represent a largely untapped resource in the mapping of constraint satisfaction regions. However appropriate sequential design heuristics remain illusive especially when the solution is likely to lie on the boundary of the valid region. As an illustration we consider a hydrology problem where, even with a simple linear objective function, learning a nontrivial valid region complicates the search for a global minimum.

## **Efficient designs for choice experiments with partial profiles**

**Heiko Grossmann**

Queen Mary University of London, UK

Stated choice experiments are a popular method for measuring how the characteristics of products or services influence consumer preferences. The method uses an experimental design to generate a number of choice sets, each of which contains a usually small number of alternatives, which are also known as options or profiles. These profiles are combinations of the levels of a set of attributes that represent the main features of, for example, the products. Typically respondents are asked to choose the most preferred option from each choice set and these categorical responses are used to estimate utility values for the attribute levels.

Recently there has been considerable interest in developing designs which may help to reduce the complexity of the choice task when there are many attributes. In order to avoid negative side effects of high task complexity, such as fatigue or information overload, in each choice set these designs only use some of the attributes in a study to describe the alternatives, which are hence called partial profiles. This presentation presents some of our analytic results on the construction of efficient designs for the situation where each choice set is a pair of partial profiles and where only the main effects of the attributes are to be estimated. Moreover, implications of these results for developing design algorithms will be explored.

## **Computing Efficient Exact Designs of Experiments Under Cost Constraints**

**Radoslav Harman**

Faculty of Mathematics, Physics and Informatics, Comenius University, Bratislava

Computing exact optimal designs of experiments with restrictions on the costs is a very challenging problem. For instance the knapsack problem, which is known to be NP-hard, is merely its simple special case. The standard computational methods of exact optimal design, including the exchange algorithms and the methods based on “rounding” approximate optimal designs, are often unsuitable for the situations with different costs of runs.

In the talk we will review several approaches to constructing efficient exact designs under cost constraints, such as a) solving the problem by “intelligent” enumeration techniques based on the branch-and-bound principle, b) using specific stochastic optimization methods related to simulated annealing, and c) finding a computationally simpler approximation of the problem providing near-optimal designs.

### **Multi-stage Optimal Design for Michaelis–Menten model**

**Linwei Hu**

University of Georgia

**Collaborators/co-authors:** Min Yang

A complication for studying optimal designs for nonlinear models is that information matrices depend on the unknown parameters. Multi-stage design, in which one estimates parameters from existing design then add new design points according to the estimates, could overcome this. However, how to implement the strategy remains challenging. First, how to construct the optimal designs in general? The current tools, which are mainly for locally optimal design, cannot be applied, at least not directly. Second, how well does the parameter estimates behave? For sequential designs, the asymptotic property of parameter estimates should be investigated more carefully. Third, how efficient are multi-stage designs compared to locally optimal designs? The purpose of this presentation is to address these issues. We developed a general approach of deriving optimal multi-stage design for a class of two-parameter models (Michaelis–Menten model, loglinear model, Klimpel’s flotation recovery model, etc.) under a broad class of optimality criteria. Focusing on Michaelis–Menten model, we investigated the efficiency of the designs as well as the large sample property of the parameter estimators. Moreover, the uniqueness of optimal design in each adaptive stage was proven, which is an interesting result and a desirable property when the closed form solution is not available in general.

### **Adaptive Probability-Based Latin Hypercube Designs for Slid-Rectangular Regions**

**Ying Hung**

Department of Statistics and Biostatistics, Rutgers University

Adaptive sampling is an effective method developed mainly for regular regions. However, experimental regions in irregular shapes are commonly observed in practice. Motivated by a data center

thermal management study, a new class of adaptive designs is proposed to accommodate a specific type of irregular regions. Because the adaptive procedure introduces biases into conventional estimators, several design-unbiased estimators are given for estimating the population mean. Efficient and easy-to-compute unbiased estimators are also introduced. The proposed method is applied to obtain an adaptive sensor placement plan to monitor and study the thermal distribution in a data center. All the supplemental materials used by this paper are available online.

### **Designs for Estimating the $ED_{50}$**

**Seung Won Hyun**

Department of Statistics, North Dakota State University, Fargo, ND 58102, USA

The  $ED_{50}$  is the dose that produces 50% of the maximum response. To estimate the  $ED_{50}$ , doses are usually selected in a design space that is restricted to be between the minimum dose and the maximum dose. In many cases, dose-response functions have a downturn at higher doses. If researchers ignore the downturn by restricting the design space up to the maximum dose, there must be some loss of information to estimating the  $ED_{50}$ . This study analyzes the loss of information and changes of designs to estimate the  $ED_{50}$  due to restricting the design space. For biologically motivated models that incorporate a downturn in the response function, c-optimal designs for estimating the  $ED_{50}$  and the c-optimal designs using the restricted design space are obtained and compared. We also present a two-stage optimal design to estimate the  $ED_{50}$  that is not effected much by restricting the design space.

### **An Application of Blocked Fractional Factorial Design for the Construction of Discrete Choice Experiments for Estimating Main Effects plus Interactions for Binary Attributes**

**Jessica Jaynes**

Department of Statistics, University of California, Los Angeles

**Collaborators/co-authors:** Hongquan Xu and Weng Kee Wong

Discrete choice experiments are used to quantify the value a respondent attaches to an attribute and assess how individuals develop preferences for particular attributes. They are used in the traditional areas in marketing, transportation, health science, and economics, and increasingly beyond these areas. However, there is limited work on the design for such studies to date.

Current construction techniques for choice experiments mainly focus on the estimation of main effects or main effects plus all two factor interactions. We present a new method for constructing discrete choice experiments using efficient resolution IV blocked fractional factorial designs from traditional experimental design. These designs allow the estimation of all main effects plus pre-selected two-factor interactions.

Our method provides smaller optimal choice experiments for estimating main effects plus pre-selected two-factor interactions with higher efficiencies at lower costs and require a shorter time to run. Using real life examples, we demonstrate our design techniques for binary attributes and choice sets of varying sizes.

## **A New Approach to the Design and Analysis of Supersaturated Experiments**

**Bradley Jones**  
SAS Institute Inc

Since supersaturated experiments have fewer runs than there are factors, the assumption of effect sparsity is crucial. Obviously, it is impossible to get unbiased estimates of all the parameters when there are more parameters than data points. This talk introduces a design approach that yields minimum bias estimation. By an extension of the basic method, I will also introduce designs that allow for unbiased estimation of the error variance under the assumption that interaction effects are negligible. Model selection is simplified as a result.

## **Constrained Optimal Experimental Design**

**Lulu Kang**  
Department of Applied Mathematics, Illinois Institute of Technology

Optimal experimental design for constrained design region are rising more often in many engineering fields. In this paper, we propose a general optimal design method which combines coordinate exchange and simulated annealing algorithms. The optimal criteria we have discussed include D-optimal designs, linear-optimal designs, and minimax and maximin space filling designs. Compared to the existing methods, the proposed method can be applied to more general constrained region, including nonlinear and nonconvex constraints. Examples are used to show the efficiency and effectiveness of proposed method.

## **Mixture Design of Quantile Regression Model for Portfolio-Invariant Capital Rule**

**Lie-Jane Kao**  
Department of Finance and Banking, KaiNan University, TaoYuan, Taiwan

According to the Basel II Accord by the Basel Committee on Bank Supervision, a bank must hold enough capital to cover up to the 99.9% percentile of the portfolios loss distribution, at the same time, portfolio-invariance, i.e., the capital charge per dollar of exposure depends on the characteristics of the borrowers instead of the composition of the portfolio, should be maintained (Basel Committee on Bank Supervision, 2006). However, an asymptotically fine-grained portfolio and a single systematic risk factor framework are required to guarantee portfolio-invariance (Gordy, 2003). When there are multiple systematic risk factors, portfolio-invariance fails to be established. This study is in an attempt to propose a portfolio-invariant capital rule in the multi-risk-factors framework based on the estimation of the 99.9% percentile hyperplane in terms of a quantile regression model. By grouping homogeneous loans in a banking portfolio into buckets according to borrowers credit ratings and sectors, efficient mixture designs with different combinations of buckets exposure weights are constructed so that the 99.9% percentile hyperplane can be accurately estimated. A simulation study is performed to illustrate the proposed portfolio-invariant approach and compared to existing adjustment technique, which fails to be portfolio-invariant, for the departure from the single systematic risk factor framework.

**Maximin Optimal and Efficient Designs for Functional MRI Experiments**  
**Ming-Hung Kao**

Arizona State University

**Collaborators/co-authors:** Dibyen Majumdar; Abhyuday Mandal and John Stufken

Previous studies on event-related functional magnetic resonance imaging experimental designs are primarily based on linear models, in which a known shape of the hemodynamic response function (HRF) is assumed. However, the HRF shape is usually uncertain at the design stage. To address this issue, we consider a nonlinear model to accommodate a wide spectrum of feasible HRF shapes, and propose efficient approaches for obtaining maximin optimal and efficient designs. We present some results that help to reduce the parameter space, and put forward an efficient algorithm for searching over a restricted class of designs for good designs. The designs that we obtained are compared with those widely used in practice.

**Equivalence of Factorial Designs with Qualitative and Quantitative Factors**  
**Tena I. Katsaounis**

Department of Mathematics, The Ohio State University, Mansfield, OH

Two symmetric fractional factorial designs with qualitative and quantitative factors are equivalent if the design matrix of one can be obtained from the design matrix of the other by row and column permutations, relabeling of the levels of the qualitative factors and reversal of the levels of the quantitative factors. In this paper, necessary and sufficient methods of determining equivalence of any two symmetric designs with both types of factors are given. An algorithm used to check equivalence or non-equivalence is evaluated. If two designs are equivalent the algorithm gives a set of permutations which map one design to the other. Fast screening methods for non-equivalence are considered. Extensions of results to asymmetric fractional factorial designs with qualitative and quantitative factors are discussed.

**Optimizing Experimental Design for Systems with Bivariate Failures under a Bivariate Weibull Function**  
**Sungwook Kim**

Department of Statistics at the University of Missouri

**Collaborators/co-authors:** Nancy Flournoy

In manufacturing industry, it may be important to study the relationship between machine component failures under stress. Examples include failures such as integrated circuits and memory chips in electronic merchandise given levels of electronic shock. Such studies are important for the development of new products and for the improvement of existing products. We assume two component failures for simplicity and assume the probability of failures increases as a bivariate Weibull function with stress. Optimal designs have been developed for two correlated binary responses using the Gumbel model, the bivariate binary Cox model and the bivariate probit model. In all these models, the covariate ranges from negative to positive infinity. In the Weibull model, the covariate is positive which is natural for experimental factors such as voltage, tension or pressure. In this paper, we discuss optimal designs under the bivariate Weibull assumptions.

## **Optimal Designs for Survival Data**

**Maria Konstantinou**

University of Southampton

**Collaborators/co-authors:** Stefanie Biedermann and Alan Kimber

Survival data are often met in industrial and biomedical “time to event” experiments. Efficient designs for such experiments are needed but the models involved are usually nonlinear making the optimal choice of design parameter dependent. We provide analytical characterisations of locally  $D$ - and  $c$ -optimal designs for a large class of parametric models thus reducing the numerical effort for design search substantially. We also determine parameter robust designs when a range of parameter values is provided. Our results are illustrated through an application to the exponential regression model in its proportional hazards parameterisation for different censoring mechanisms. We demonstrate that, unlike traditional designs, the designs found perform well across a broad range of scenarios. We also consider designs constructed using a semi-parametric approach for the Cox proportional hazards model. Initial results indicate that the parametric and semi-parametric approaches produce almost identical designs.

## **Information in a Two Stage Adaptive Design**

**Adam Lane**

University of Missouri

**Collaborators/co-authors:** Ping Yao and Nancy Flournoy

In *adaptive optimal designs*, each stage uses an optimal design evaluated at maximum likelihood estimates that are derived using cumulative data from all prior stages. This dependency affects the properties of maximum likelihood estimates. To illuminate the effects, we assume for simplicity that there are only two stages and that the first stage design is fixed. The information measure most commonly used in the optimal design literature is compared with Fisher’s information. To make the analysis explicit, random variables are assumed to be normal with a one parameter exponential mean function. With this model, several estimates of information are compared and a procedure for selecting the proportion of subjects allocated to stage 1 is recommended.

## **Designing Physical and Computer Experiments That Minimize the Bayesian Integrated Mean Square Prediction Error**

**Erin R. Leatherman**

The Ohio State University

**Co-authors:** Angela M. Dean and Thomas J. Santner

A computer experiment uses a computer simulator based on a mathematical model of a physical process as an experimental tool to determine “responses” or “outputs” at a set of user-specified input design points. When it is of interest to predict simulator output over the entire input space, classical design criteria for computer experiments select designs that are space-filling. This research investigates an alternative process based design criterion for this purpose which minimizes the Bayesian Integrated Mean Square Prediction Error (BIMSPE). The BIMSPE is calculated assuming a hierarchical Bayesian model for the unknown output function. In settings where

computer simulators are able to describe the true mean of an associated physical experiment, physical observations can be used to calibrate the simulator model. This research uses the minimum BIMSPE criterion to find physical and simulator designs which allow for good prediction of the true mean physical response with the calibrated simulator.

### **Fractional Factorial Designs with Groups of Factors**

**Ryan Lekivetz**

UBC Okanagan

**Collaborators/co-authors:** C. Devon Lin

The concept of resolution in the study of fractional factorial designs has a long-standing tradition. With prior knowledge of some of the factors, fractional factorial designs of variable resolution provide higher resolution among certain groups of factors, allowing for flexibility in estimability and projection properties. With knowledge about certain interactions, we extend our consideration beyond resolution. We study the existence and construction of such designs, and discuss the applicability of them.

### **Optimal Experimental Design for Population Pharmacokinetic/pharmacodynamic Studies**

**Sergei Leonov**

Vertex Pharmaceuticals Inc.

Optimal design of population pharmacokinetic/pharmacodynamic (PK/PD) studies has received considerable attention in the literature and software development over the last decade. In this presentation I outline the key components of the methodology, describe approximation options for the individual Fisher information matrix, and discuss various population design software tools which include PkStaMp library for the construction of  $D$ -optimal sampling schemes for compartmental PK and combined PK/PD models. Examples of how the software was utilized for several studies are provided.

### **Design of experiments when gradient information is available**

**Yiou Li**

Illinois Institute of Technology

**Collaborators/co-authors:** Fred J. Hickernell

When computing a function value via numerical simulation is expensive, obtaining gradient values simultaneously can improve model efficiency. Consider the design problem for linear regression models fitted using both function and gradient data. When the form of regression model is unknown, for multi-factor models with polynomials of arbitrary degree, it is shown that low discrepancy designs guarantee moderate integrated mean square error and outperform Latin hypercube design in some cases. If the form of regression model is known, then the optimal design can be computed using semi-definite programming. These optimal designs differ from those where only function values are used.

## Using Genetic Algorithms to Design Experiments

C. Devon Lin

Department of Mathematics and Statistics, Queen's University

**Collaborators/co-authors:** C. M. Anderson-Cook, M. S. Hamada, L. M. Moore and R. R. Sitter

Genetic algorithms (GA's) have been used in many disciplines to optimize solutions for a broad range of problems. In nearly the last 20 years, the statistical literature has seen an increase in the use and study of this optimization algorithm for generating optimal designs in a diverse set of experimental settings. These efforts are due in part to an interest in implementing a novel methodology as well as the hope that careful application of elements of the GA framework to the unique aspects of an experimental design problem might lead to an efficient means of finding improved or optimal designs. In this paper, we explore the merits of using this approach, some of the aspects of design that make it a unique application relative to other optimization scenarios, and discuss elements which should be considered for an effective implementation. We conclude that the current GA implementations can but do not always provide a competitive methodology to produce substantial gains over standard optimal design strategies. We consider both the probability of finding a globally optimal design as well as the computational efficiency of this approach. However, we encourage continued research focused on the representation of the optimal design problem to take advantage of the unique elements of GA's and on rigorous demonstrations of their superiority over standard optimal design strategies.

## Heterogeneous Designs for Hierarchical Choice Models

Qing Liu

University of Wisconsin-Madison

We investigate heterogeneous designs for conjoint choice experiments where different designs (individual designs) are administered to different groups of respondents. The combination of all these individual designs (combined design) is used for the estimation of hyperparameters in hierarchical choice models. Previous research on heterogeneous designs, such as that of Sandor and Wedel (*Journal of Marketing Research* 42 (2005) 2, 210-218), assumes the same objective function for the construction of both the individual designs and the combined design. We propose to construct the heterogeneous designs so that the individual designs are efficient for estimation of individual-level parameters while the combined design is efficient for the estimation of hyperparameters. When covariates information such as demographic groups is available on individual respondents, the individual designs can be further customized according to the covariates. We derive the objective functions and develop a computational algorithm to construct such designs. Simulation results show that these designs achieve significant gains in efficiency when compared with benchmark designs.



## Calibrating Star Formation

Jason Loeppky

University of British Columbia

**Collaborators/co-authors:** Erik Rosolowsky

The process of star formation is the fundamental agent at determining how an isolated galaxy like our own evolves over the course of the Universe. Many physical processes contribute to star formation (gravitation, magnetism, chemistry, radiation and fluid dynamics). However, it is not understood exactly how these effects shape the process of star formation. Physical observations from radio telescopes provide some insight into to the process of star formation but alone do not provide the necessary information to understand exactly how the physical process evolves. Properly designing an experiment to study star formation is complicated by many factors. First a single run of the computer model can take upwards of five thousand hours, secondly the natural parameterization of the input space is correlated and non-rectangular in addition some of the input variables are evolve during the code runs meaning that the inputs of the computer code are observed with error. Lastly, comparing code runs to physical observations is complicated by two things, first we must compare a three dimensional data cubes and secondly simple euclidean distance between these cubes is not the correct measure of similarity between these two objects. In this talk we will discuss some recent work on the design and analysis of complex experiments to study star formation. The ultimate goal of this study is to provide a physically meaningful discription of how stars evolve.

## Construction of Neighbor Designs with $v = 2m$

Nutan Mishra

University of South Alabama

Rees neighbor designs with complete binary blocks can also be seen as solutions to children's round dance problems with  $v = k = 2m + 1$  in  $m$  blocks. Obviously such designs could be constructed only for odd number of treatments. In the present article we discuss the existence and construction of neighbor designs with  $v = 2m$  and with complete as well as incomplete blocks. In these constructions of series of neighbor designs there is no restriction on the number of blocks instead we try to keep the value of  $lnbr$ , the number of times two treatments occur together as neighbors, as small as possible. For  $v = 2m$ , the minimum value  $lnbr$  can assume is 2 and the other higher values are multiples of two. The neighbor designs and generalized neighbor designs are constructed by the following methods: by generating base blocks, from the existing BIB designs and PBIB designs by rearranging the base blocks, by rearranging the treatments within blocks of the design and by composition of two designs. Alternative non-BIB solutions are discussed for some of the designs with  $k = 4$ .

## Weighting Schemes and Optimal Design

J. P. Morgan

Virginia Tech

Collaborators/co-authors: J. W. Stallings

Weighted optimality criteria allow experiments to be designed so to place increased emphasis on estimation of those functions of the parameters that are of greater interest. Here design weighting is investigated for linear models. Focus is on the commonly encountered model  $y = A_d\tau + L\beta + e$  in which  $A_d$  is the design matrix to be selected, the parameters of interest are  $\tau$ , the matrix  $L$  is fixed by the experimental setup, and  $\beta$  is comprised of nuisance parameters including an intercept. If  $C_d$  is the information matrix for estimation of  $\tau$ , then  $C_{dW} = W^{-1/2}C_dW^{-1/2}$  is a weighted information matrix that for any conventional criterion  $\Phi$  induces a weighted criterion  $\Phi_W$  via  $\Phi_W(C_d) = \Phi(C_{dW})$ . The weight matrix  $W$  can be any symmetric, positive definite matrix. Among the results established are: (i) for any desired assignment of (positive) weights to any full rank set of linearly independent, estimable functions of  $\tau$  there is a corresponding weight matrix  $W$ ; (ii) every admissible design is weighted E-optimal with respect to some weighting; (iii) optimal design for a reparameterized model is equivalent to weighted optimality for the original model. Families of weight matrices  $W$  are explored according to features they encompass. Applications include to confounded fractions and to fractions under a baseline parametrization. Connections are drawn to other work including Kao, Yates, Lewis, and Dean (Statist. Sinica 5 (1995), 593-598) and Bortnick, Dean, and Hsu (J. Statist. Plann. Inference 129 (2005), 109-124).

## Physical Experimental Design in Support of Computer Model Development

Max D. Morris

Iowa State University

Deterministic computer models of physical systems are often based on theory about the modeled system. For example, equations that represent the dynamics of a chemical process, a communications network, or the global climate are developed, appropriately linked, and computer models are written that solve these systems for specific instances described by model inputs. However, in many cases the known theory is incomplete to write the entire model from first principles, and some degree of physical experimentation is needed to estimate key functions. A useful mental picture is to think of a program in which one subroutine returns the value of an empirical model fitted to experimental data, but for which the rest of the program represents “known physics”. In this talk, the question of how the design of such (physical) experiments may be undertaken with the goal of producing a good computer model.

**Fundamental Theorems of Quaternary-code Designs**  
**Frederick Kin Hing Phoa**

Institute of Statistical Science, Academia Sinica, Taiwan R.O.C.

The study of good nonregular fractional factorial designs has received significant attentions over the last two decades. Recent research indicates that designs constructed from quaternary codes (QC) are very promising in this regard. The present talk aims at exploring the fundamental structure and developing the underlying theorems of QC designs. Theorems and their corollaries characterize the wordlengths and aliasing indexes of the words when a general  $(1/4)^p$ -fraction QC design is given. In addition, for designs of large dimensions, some theorems about the structure periodicities of a general  $(1/4)^p$ -fraction QC design are stated.

**Catalogs of Split-Plot Type Designs for Physical Prototype Testing**  
**André Luís S. de Pinho**

Department of Statistics, Universidade Federal do Rio Grande do Norte, Brazil

**Collaborators/co-authors:** Linda L. Ho and Carla A. Vivacqua

Companies always seek strategies to shorten product development and reduce time-to-market. Although new technologies allow for less effort in prototyping, physical testing still remains an important step in the product development cycle. Well-planned experiments are useful to guide the decision-making process. During the design of an experiment one of the challenges is to balance limited resources and system constraints to obtain useful information. It is common that prototypes are composed of several parts, with some parts more difficult to assemble than others. And, usually, there is only one piece available of each part type and a large number of different setups. Under these conditions, designs with randomization restrictions become attractive approaches. Considering this scenario, a new and additional criterion to construct two-level split-plot type designs is presented. Designs with a small number of setups of the more difficult parts, which are especially useful for screening purposes in physical prototype testing, are discussed. Theoretical properties of the designs are provided and it is shown how to appropriately analyze the data through a real application in testing car prototypes. As a tool to practitioners, catalogs of selected 32-run split-split-plot and split-split-split-plot designs are presented.

**Tractable Functional Response Modelling with Processes with Non-Separable  
Covariance Functions**  
**Matthew Plumlee**

The Georgia Institute of Technology

**Collaborators/co-authors:** V. Roshan Joseph

Growth in the technology of sensors, data acquisition, and data storage has made it increasingly common to receive samples in the form of profile or image data, which require the modelling of an underlying functional response. Gaussian Process models have become increasingly popular to

model functional responses; these give the flexibility needed to deal with non-linear functions. However, fitting these models requires computationally expensive matrix inversion or decomposition that costs on the cubic order. For systems with functional responses, this problem is exacerbated, as the amount of data grows very quickly with the number of profiles or images observed. Many works in the functional response domain have included the separability and stationarity assumptions on the covariance function of the GP model to ease the computational burden. This assumption allows one to separately perform matrix operations in the spatial and temporal dimensions, reducing the computational burden. However, in many applications, separability is an invalid assumption. Toward the aim of relaxing the separability assumption in large data sets, this work proposes a method to model these functions without the separability assumption while maintaining the computational advantages.

### **Optimal designs for prediction of individual effects in random coefficient regression models**

**Maryna Prus**

Otto-von-Guericke University, Magdeburg, Germany

**Collaborators/co-authors:** Rainer Schwabe

In the last years random coefficient regression models become more popular in many application fields, especially in biosciences. Besides the estimation of population parameters describing the mean behavior of the individuals under investigation a prediction of the response for the specific individuals may be of interest. For the determination of optimal designs for estimating the population parameters some analytical and practical results may be found in the literature. Concerning prediction of the individual responses the theory developed by Gladitz and Pilz (*Statistics* (1982) 13, 371–385) for optimal designs requires the prior knowledge of the population parameters.

Here the theory and solutions for prediction of individual response in the case of small to moderate numbers of individuals will be presented for the practical relevant situation of unknown population parameters. While the optimal designs will differ from the Bayesian designs proposed by Gladitz and Pilz (1982), if the individual responses are of interest themselves, the Bayesian designs turn out to remain their optimality, if differences between individuals are to be investigated. The obtained theoretical results will be illustrated by a simple numerical example.

### **Probability-Based Optimal Design with Separation Problems**

**M. Lutfor Rahman**

Queen Mary, University of London

**Collaborators/co-authors:** Steven G. Gilmour

Separation is a common problem in models with binary responses when one or more covariates perfectly predicts some binary outcome. The separation problem leads to convergence difficulties as well as non-existence of likelihood estimates of model parameters. Some methods have been proposed in literature to deal with the separation problems. In this paper we propose a new probability-based optimality criterion ( $P_s$ ) that would reduce the problem of separation and thus maximize the probability of the existence of likelihood estimates.

## **Optimal Block Designs with Autocorrelation**

**Emily Rands**

University of Southampton

**Collaborators/co-authors:** Dave Woods

Block designs are used when the runs of a particular experiment can be partitioned into different groups. For random block designs, there are two random effects assumed and therefore there are two variance components:  $\sigma_\epsilon^2$ , accounting for the variation between runs within a block; and  $\sigma_\gamma^2$  accounting for the variation between blocks. When both random effects are assumed to come from independent distributions, an exchangeable correlation structure results, with two runs within a block being more similar than two runs from different blocks.

We consider the effect on the choice of design of assuming that the within-block errors follow a distribution with an autoregressive correlation pattern of order 1. An AR(1) correlation structure assumes that the dependency between observations within a block decreases as the “distance” between experimental units increases. It is appropriate when there is a suitable distance metric for the experimental units, such as in agricultural field trials or industrial and scientific experiments in well-plates or arrays. Using a coordinate exchange algorithm, we find D-optimal designs for different degrees of autocorrelation and assess the robustness of these designs, as well as designs found assuming exchangeable correlation, to misspecification of the autocorrelation.

## **GPfit: An R library for a Computationally Stable Approach to Gaussian Process Interpolation of Deterministic Simulators**

**Pritam Ranjan**

Acadia University

**Collaborators/co-authors:** Hugh Chipman

Gaussian process (GP) models are commonly used for emulating computationally expensive computer simulators. Fitting a GP model requires the computation of the inverse and determinant of the spatial correlation matrix,  $R$ . The near-singularity of  $R$  can cause instability in the computation of its determinant and inverse. The popular approach to overcome near-singularity is to introduce a small nugget (or jitter) parameter in the model that is estimated along with other model parameters. The inclusion of a nugget in the model often causes unnecessary over-smoothing of the data. We propose a lower bound on the nugget that minimizes the over-smoothing and an iterative regularization approach to construct a predictor that further improves the interpolation accuracy. The likelihood optimization in fitting GP can be computationally intensive. We propose an alternative parameterizations of the likelihood for ease of optimization. Moreover, we developed an R package called GPfit that implements the proposed methodology.

**Optimal Design for Dose-Response Trials, with Application to Adaptive Trials**  
**Russell Reeve**  
Quintiles, Inc.

Dose-response models are often fit using the four parameter Hill model. The  $D$ -local optimal design is developed, along with a Bayesian optimal design based on the Bayesian prior for the model parameters. Optimal designs or other criteria are also investigated, including  $c$ - and  $I$ -optimality. The Bayesian  $D$  optimality is used to propose an adaptive trial design, where the updated prior for the parameters are used to construct a new optimal design point for the next set of observations. The efficiency of the adaptive trial for estimating the dose-response curve is compared to that of a fixed design based on a single prior. Simulation studies are used to demonstrate the characteristics that can be expected from such an adaptive trial.

**Multiplicative Algorithm for Computing Optimum Designs.**

**Licesio J. Rodríguez-Aragón**

Universidad de Castilla-La Mancha, Ciudad Real, Spain

**Collaborators/co-authors:** Roberto Dorta-Guerra, Raúl Martín-Martín and Mercedes Fernández-Guerrero

Multifactor models are present in industry and in biological experiments; therefore optimum designs are a valuable tool for experimenters, leading to estimators of the parameters with minimum variance. Several algorithms have been devised for determining optimal designs including a class of Multiplicative Algorithms for determination of optimal weights.

$$\xi(x_j)^{(r+1)} = \frac{\xi(x_j)^{(r)}g(h_j^{(r)}, \delta)}{\sum_{i=1}^J \xi(x_i)^{(r)}g(h_i^{(r)}, \delta)}$$

where  $r = 0, 1, \dots$  is the iteration number,  $g(x, \delta)$  is positive, strictly increasing,  $\partial g(x, \delta)/\partial x > 0$  and, if  $\delta = 0$ ,  $g(x, \delta)$  is constant, being either  $h_j = \partial\phi/\partial\xi(x_j)$  or the vertex directional derivatives. This algorithm has been devised for several problems due to ease of implementation and monotonic convergence for some optimality criteria. A generalization of the Multiplicative algorithm to find locally optimum designs for non-linear multifactor models is here proposed. The method consists of transforming a conceived set of design points over a finite interval into proportions of the design interval defined by the sub-intervals between successive points.

Examples for different modifications of the  $pVT$  models, as the Tait equation, or enzyme inhibition models are here presented. Efficiencies of real experimental designs are computed and suitable more efficient experimental designs, satisfying experimental demands are also proposed. Traditional algorithms as the Wynn-Fedorov scheme have also been adapted to obtain optimum designs for non-linear multifactor models. Comparisons of the behavior of these algorithms is performed for  $D$ - and  $A$ - optimality criteria and combinations of these algorithms are here presented.

## **Approximate Model Spaces for Model-Robust Experiment Design**

**Byran J. Smucker**

Miami University, Oxford, OH

**Collaborators/co-authors:** Nathan Drew

Optimal experiment design, utilizing criteria such as D-optimality, requires that the model form be specified before the experiment is conducted. The resulting design is quite dependent upon this specification. To reduce or eliminate this dependence, various model-robust design approaches have appeared in the literature. One standard approach is to design with a set of model forms in mind instead of just one so that the design is robust for the models in the set. However, the size of these sets can easily grow so large that it is difficult or computationally infeasible to construct the model-robust designs. In this talk, we present a method that allows construction of designs that are robust for large model sets while requiring only a fraction of the computational effort. This is accomplished by choosing only a small subset of the models in the entire set and constructing a design that is explicitly robust to this subset. The designs constructed thusly are quite competitive with designs that are obtained by utilizing the entire model space.

## **Designing for Attribute-Level Best-Worst Choice Experiments**

**Deborah Street**

School of Mathematical Sciences, University of Technology, Sydney

**Collaborators/co-authors:** Stephanie Knox

In a traditional discrete choice experiment, respondents indicate which one of a set of products (services or profiles) they think is best, and they usually do this for a number of sets. However this does not allow the experimenter to gain any information about the relative contribution to the utility of each of the levels in a profile. To rectify this deficiency, researchers can show respondents a *profile*, described by the levels of a number of attributes, and ask each respondent to choose the best and the worst feature (attribute-level) of the profile. Such a task is called an *attribute-level best-worst choice task*. Using the *D*-optimality criterion, we show that resolution 3 fractional factorial designs perform as well as the complete factorial design in attribute-level best-worst choice experiments, assuming both that all attribute levels are equally attractive and that only main effects of attribute levels are to be used to explain the results. We close by describing an attribute-level best-worst choice experiment which was given to both a sample of women of reproductive age and to a sample of GP providers to compare how they value particular features of contraceptive products. Simulation results indicate that the chosen design was adequate to return consistent estimates in this attribute-level best-worst choice experiment.

## **Main Effects Plus One Plans for $2^m$ Factorial Experiments with Even $m$**

**Hooshang Talebi**

Department of Statistics, University of Isfahan, Isfahan

**Collaborators/co-authors:** Elham Jalali

A main effect plus one plan, *MEP.1*, is a design which is able to identify and estimate a nonzero interaction effect along with estimating the general mean and main effects. Construction of such

a plan for a  $2^m$  factorial experiment has been considered by several authors. Recently, the *MEP.1* plans is given for all odd  $m$  with  $N = 2m$  runs,  $m > 4$ . In this paper, we present a new series of *MEP.1* plans for all even  $m = 2t$ ,  $2 \leq t \leq 14$ , with  $N = 2(m + 1)$  runs, which is compatible with the number of runs in the previous series for odd  $m$ , however, is superior with respect to the well coherent structural form.

**An Asymptotic Theory for Gaussian Process Models in Deterministic Systems and Its Application to Calibration in Computer Experiments**

**Rui Tuo**

Chinese Academy of Sciences and Georgia Institute of Technology

**Collaborators/co-authors:** C. F. Jeff Wu

One major problem in computer experiments is how to build surrogate models for expensive computer simulations. To model deterministic computer outputs, interpolators, like the kernel interpolation method, are commonly used. Gaussian process models can be viewed as a statistical extension of the kernel interpolation, which allows for the estimation of the model parameters via the maximum likelihood method. In this work, key asymptotic properties of these MLE estimators are studied when the true function of interest is deterministic. These results have a direct application to the calibration problem in computer experiments. We give a formal definition of the calibration problem and show that the method by Kennedy and O'Hagan (*Journal of the Royal Statistical Society, Series B* 63 (2001) 425–464) causes an inconsistent calibration due to an overfitting problem. We also show that, after a slight modification of the estimation procedure, both calibration and interpolation can achieve asymptotic consistency.

**Design and Analysis of Unreplicated Mixed Two-Level and Four-Level Split-Plot Type Experiments**

**Carla A. Vivacqua**

Department of Statistics, Universidade Federal do Rio Grande do Norte, Brazil

**Collaborators/co-authors:** Linda L. Ho and André Luís S. de Pinho

We use the method of replacement to construct mixed two-level and four level split-split-split-plot designs from  $2^{k-p}$  designs and choose designs according to the criteria of minimum number of setups of the harder-to-change factors and minimum aberration. An analysis strategy for these designs is presented. We consider an experiment to improve the performance of a Baja car with mixed two-level and four-level factors as an illustration.

The Society of Automotive Engineers (SAE) promotes the development of college students through car competitions all over the world. The objective of the experiment discussed here is to maximize the performance of a competition vehicle on two tests carried out on a paved street with an asphalt layer. The first one, called acceleration test, evaluates the time that the vehicle takes to cover a distance of 30 meters starting from a complete stop. The second one, called velocity test, measures the final velocity reached by the Baja at the 100 meters mark. The ideal setup would be the one that simultaneously provides the maximum velocity at 100 meters mark and the minimum time to cover the first 30 meters.



## **Optimal Block Designs for Generalized Linear Mixed Models**

**Tim Waite**

University of Southampton

**Collaborators/co-authors:** Dave Woods and Tim Waterhouse

For an experiment measuring a discrete response, a generalized linear model such as logistic or log-linear regression is typically used to model the data. However, in certain circumstances it may be more appropriate to employ random effects to model the blocks as being sampled from a population. Inclusion of these terms leads to a generalized linear mixed model (GLMM). The use of GLMMs allows the possibility of predicting responses in future blocks, and also permits estimation of whole-plot factors in split-plot experiments. Obtaining designs for these models is complicated by the fact that the information matrix, on which most optimality criteria are based, is computationally expensive to evaluate (indeed if one computes naively, the search for an optimal design is likely to take several months). The estimation literature contains proposals for several different analytical approximations for use with GLMMs in lieu of the full marginal likelihood. In this talk, we explore the use of these approximations as the basis of surrogates for the true information matrix when producing designs. This reduces the computational burden substantially, and enables us to obtain designs within a much shorter time frame. However, other issues also need to be considered such as the accuracy of the approximations and the dependence of the optimal design on the unknown values of the parameters.

## **Analysis of Cell Adhesion Experiments Based on Hidden Markov Models**

**Yijie Wang**

Georgia Institute of Technology

**Co-authors:** Ying Hung and Jeff Wu

Cell adhesion plays an important role in physiological and pathological processes. It is mediated by specific interactions between cell adhesion proteins (called receptors) and the molecules to which they bind (called ligands). This study is motivated by cell adhesion experiment conducted at Georgia Tech, which uses decrease/resumption of thermal fluctuations of a biomembrane probe to pinpoint association/dissociation of receptor-ligand bonds. More than one type of bond is commonly observed and they correspond to different fluctuation decrease due to their string strength difference. Existing approach is not robust in estimating the association/dissociation points and can only detect one type of bond. A hidden Markov model is developed to tackle the problems. It works by assuming that the probe fluctuates differently according to the underlying binding states of the cells, i.e., no bond or distinct types of bonds. These states are unobservable but their changes can be captured by a Markov chain. Applications of the proposed approach to real data demonstrate robustness and accuracy of estimating bond lifetimes and waiting times, which form basis for estimation of kinetic parameters.

## **Optimal Design for a New Bounded Log-linear Regression Model**

**HaiYing Wang**

Department of Statistics, University of Missouri - Columbia

**Collaborators/co-authors:** Andrey Pepelyshev and Nancy Flournoy

Wang and Flournoy (<http://www.newton.ac.uk/preprints/NI12001.pdf>) developed estimation procedures for a new bounded log-linear regression model, an alternative to the four parameter logistic model, which has bounded responses and nonhomogeneous variance. We show that the information matrix based designs are independent of the two parameters representing the boundaries of the responses, but they depend on the variance of the error. Theoretically, we obtain that information matrix based optimal designs for this model consists of at most five points including the two boundaries of the design space. Furthermore, if the error variance is known and big, we prove that the D-optimal design is a two points design with equal weights on the two boundaries. Numerical examples are provided.

## **Optimal Designs for Binary Dose-response Models with Control Mortality**

**Tianhua Wang**

University of Missouri - Columbia

The binary dose-response models are used a lot in bioassay, where response is often death, termed control mortality. For the three-parameter binary dose-response models that incorporate control mortality, although there exist some numerical results for locally and Bayesian optimal designs in recent publications, there lacks of systematic study of optimal designs. In this project, we study the general format of optimal designs for this model. The general format makes it relatively easy to derive some specific optimal design and develop more efficient algorithms. The results are also valid for multistage designs.

## **Some Problems in Robustness of Design**

**Doug Wiens**

Statistics Centre; Dept. of Mathematical and Statistical Sciences; University of Alberta

Robustness of design is an area in which there remain numerous problems that are easily stated but frustratingly difficult to solve. Some arise very early in the development – straight line regression – and persist in more complex models. Here I will discuss three such problems in the SLR context. If time allows I will talk more generally about the role that robustness might play in more complex situations.

## **Efficiencies of Designs in the Simple Linear Regression Model with Correlated Errors**

**Adrian Wilk**

TU Dortmund University, Germany

**Collaborators/co-authors:** Joachim Kunert

We consider the simple linear regression model with correlated errors. Our model assumes that the correlation between two observations depends on the distance of the corresponding design points. In particular, we analyze designs with three design points which are compared with respect to their D-efficiencies. For the situation that the correlation parameter is known we present lower bounds for the D-efficiencies. Furthermore we present a simulation study for the case of an unknown correlation parameter.

## **Meta-Heuristic Algorithms for Generating Optimal Experimental Designs**

**Weng Kee Wong**

Department of Biostatistics, Fielding School of Public Health, UCLA

**Collaborators/co-authors:** Ray-Bing Chen, Jia-heng Qiu and Weichung Wang

Particle swarm optimization (PSO) is a relatively new, simple and powerful way to search for an optimal solution. It is widely used in many applied fields. The method works quite magically and frequently finds the optimal solution or a nearly optimal solution after a few iterations. There is virtually no assumption required for the method to perform well and the user only needs to input a few easy to work with tuning parameters.

I use mixture experiments and nonlinear models in the biological sciences to demonstrate that PSO can find different kinds of optimal designs quickly, including mini-max types of optimal designs where effective algorithms to find such designs have remained elusive until now. Dose response studies will serve as illustrative applications.

## **Three-phase Sequential Design for Sensitivity Experiments**

**C. F. Jeff Wu**

Georgia Institute of Technology

**Collaborators/co-authors:** Yubin Tian

In sensitivity testing the test specimens are subjected to a variety of stress levels to generate response or non-response. These data are used to estimate the critical stimulus (or threshold) level of the experimental object. Because of its versatile applications, several sensitivity testing procedures have been proposed and used in practice. There remains the outstanding question of finding an efficient procedure, especially when the sample size is small and the interest lies in the extreme percentiles. In the paper we propose a novel three-phase procedure, dubbed 3pod, which can be described as a trilogy of “search-estimate-approximate”. A core novel idea is to choose the design points to quickly achieve an overlapping data pattern which ensures the estimability of the underlying parameters. Simulation comparisons show that 3pod outperforms existing procedures over a range of scenarios in terms of efficiency and robustness.

## **Optimal Designs for Accelerated Life Testing (ALT) Experiments with Step-stress Plans**

**Xiaojian Xu**

Brock University

In this paper, we discuss the optimal and robust designs for accelerated life testing when a step-stress plan is performed. We consider an ALT model consisting of a Weibull life distribution with a log-linear life-stress relationship, and a cumulative exposure model for the effect of changing stress. Taking into account that the shape parameter of the Weibull life distribution also possibly varies when stress level changes, we have derived the optimal designs in order to minimize the asymptotic variance of the estimator for the reliability of a product at the normal use stress level and at a given time. Furthermore, due to extrapolation always involved in ALT, any departure from the assumed life-stress relationship would cause the resulting designs far from being optimal. Therefore, the possible departure from assumed life-stress relationship has been further considered. Assuming both the fitted and true life-stress relationship to be polynomials, we have investigated the robust designs for censored data in order to reduce the effect of the fitted model being possibly incorrect with a minimum loss of the efficiency.

## **Optimal Designs for $2^k$ Factorial Experiments with Binary Response**

**Jie Yang**

University of Illinois at Chicago

**Collaborators/co-authors:** Abhyuday Mandal and Dibyen Majumdar

We consider the problem of obtaining locally D-optimal designs for factorial experiments with binary response and  $k$  qualitative factors at two levels each. Yang, Mandal and Majumdar (*Statistica Sinica* 22 (2012), 885-907) considered this problem for  $2^2$  factorial experiments. In this talk, we generalize the results for  $2^k$  designs and explore in new directions. We obtain a characterization for a design to be locally D-optimal. Based on this characterization, we develop efficient numerical techniques to search for locally D-optimal designs. We also investigate the properties of fractional factorial designs and study the robustness, with respect to unknown parameters, of locally D-optimal designs. Using prior distribution on the parameters, we investigate EW D-optimal designs, that are designs which maximize the determinant of the expected information matrix. It turns out that these designs are much easier to find and still highly efficient compared to Bayesian D-optimal designs, as well as quite robust.

## **Universally Optimal Crossover Designs at the Presence of Subject Dropout: An Approximate Design Theory**

**Wei Zheng**

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Subject dropout is very common in practical applications of crossover designs. However, there is very limited literature of experimental design taking this into account. Optimality results have not yet been well established due to complexity of the problem. This paper establishes

feasible necessary and sufficient conditions for a crossover design to be universally optimal in approximate design theory under the presence of subject dropout. These conditions are essentially linear equations with respect to proportions of all possible treatment sequences being applied to subjects and hence they can be easily solved. A general algorithm is proposed to derive exact designs which are shown to be efficient and robust.

### **Mixture discrepancy for quasi-random point sets**

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**Collaborators/co-authors:** Kaitai Fang, Jianhui Ning

There are various discrepancies that are measures of uniformity of a set of points on the unit cube in high dimensional space. The discrepancies have played an important role in quasi-Monte Carlo Methods. Each discrepancy has its own characteristic and some weakness. In this paper we point out some unreasonable phenomenon of the common used discrepancies in the literature such as the  $L_p$ -star discrepancy, the center  $L_2$ -discrepancy (CD) and the wrap-around  $L_2$ -discrepancy (WD). Then, a new discrepancy, called as mixture discrepancy (MD), is proposed. As shown in the paper that the mixture discrepancy is more reasonable than CD and WD for measuring the uniformity through different aspects such as the intuitive view, the uniformity of subdimension projection, the curse of dimensionality and the geometry property of the kernel function. Moreover, the relationships between MD and other design criteria such as balance pattern and generalized wordlength pattern are also given.

### **Optimal clinical trial designs to detect treatment-biomarker interaction**

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Biomarkers play a crucial role in the design and analysis of clinical trials for personalized medicine. One major goal of these trials is to derive an optimal treatment scheme based on each patient's biomarker level. Although completely randomized trials may be employed, a more efficient design can be attained when patients are adaptively allocated to different treatments throughout the trial using biomarker information. Therefore, we propose a new adaptive allocation method based on using multiple regression models to study treatment-biomarker interactions. We show that this perspective simplifies the derivation of optimal allocations. Moreover, when implemented in real clinical trials, our method can integrate all the covariates which may not be related to the treatment-biomarker interaction into a single mode for a joint analysis. Our general idea can be applied to diverse models to derive optimal allocations. Simulation results show that both the optimal allocation and the proposed design can lead to a more efficient trial, where the required sample size can be reduced by 10% compared to traditional procedures.