Advances in Adaptive and Optimal Experimental Designs (December 2 and 3, 2020)
(online satellite meeting to GMDS & CEN-IBS 2020)

Organizing committee: Nancy Flournoy (flournoyn@missouri.edu), Adam Lane (Adam.Lane@cchmc.org), and Sergey Tarima (starima@mcw.edu)

All times below are US eastern time [Pacific time -3, Central time -1, Time in Germany, Italy, Slovenia +6].

Dec 2nd, Advances in Experimental Design: Theory and Applications (Session organizer: Sergey Tarima)

11:00-11:10 Introduction
11:10-11:40 Radoslav Harman (CANCELLED)
11:40-12:10 Adam Lane
12:10-12:20 Break
12:20-12:50 Caterina May
12:50-13:20 Maryna Prus
13:20-13:50 Chiara Tomassi
13:50-14:20 Informal Discussion

Dec 3rd, Random Sample Size in Medical Research (Session organizer: Adam Lane)
11:00-11:10 Introduction
11:10-11:40 Thomas Asendorf
11:40-12:10 Nancy Flournoy
12:10-12:20 Break
12:20-12:50 Aniko Szabo
12:50-13:20 Sergey Tarima
13:20-13:50 Informal Discussion

Title: Tall data subsampling and outlier detection via optimal experimental design
Authors: Radoslav Harman and Samuel Rosa
Affiliation: Comenius University Bratislava, Bratislava
Abstract:
A dataset is called "tall" if it contains a very large number of observations (corresponding to, say, a million of rows of the data matrix), but each observation has only a moderate dimension (the data matrix has at most a few tens of columns). In the talk, we will propose a method that utilizes the notion of the minimum-volume enclosing ellipsoid (MVEE) to construct an information-based subsample and identify outliers of a tall dataset. Our method alternates between (i) using the REX algorithm [1] for D-optimal design to calculate the MVEE on an auxiliary subset of the original data and (ii) removing redundant data-points based on the "partial" MVEEs determined by the method of [2].
References:
[1] Harman R, Filová L, Richtárik P (2020): A Randomized Exchange Algorithm for Computing Optimal Approximate Designs of Experiments, Journal of the American Statistical Association Vol. 115, pp. 348-361
[2] Harman R, Pronzato L (2007): Improvements on removing non-optimal support points in D-optimum design algorithms, Statistics & Probability Letters, Volume 77, pp. 90-94

Keywords: D-optimal design, Big data, Subsampling, Outliers, Minimum-volume enclosing ellipsoid

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Title: Optimizing the number of locations per sub-region in multi-environment trials

Authors: Maryna Prus, Hans-Peter Piepho

Affiliation:

Abstract:

New crop varieties are usually evaluated for their performance in a target population of environments (TPE). This evaluation requires conducting randomized field trials at several environments sampled from the TPE. Such trials are called multi-environment trials (MET).

If the TPE is large and can be suitably stratified along geographical borders or agro-ecological zonations, it may be advantageous to subdivide the TPE into sub-regions. If the same set of genotypes is tested at a number of locations in each of the sub-regions, a linear mixed model may be fitted with random genotype-within-sub-region effects that allows estimating a genotype's average performance in each sub-region using best linear unbiased prediction.

The design of MET for a sub-divided TPE involves two decisions: (1) The total number of environments at which to conduct the trials and (2) the allocation of this total number of environments to the different sub-regions. The present work is devoted to the second decision: We propose an analytical approach for computation of optimal allocation numbers per sub-region with respect to the prediction of the genotype effects.

Keywords:

Title: Optimal selection from a Big Dataset

Authors: Tommasi Chiara and Deldossi Laura

Affiliation: University of Milan

Abstract:

Big Data are generally huge quantities of digital information accrued automatically and rarely result from properly planned population surveys. Despite this, a Big Dataset is conceived as a collection of information concerning a finite population. Since the analysis of an entire Big Dataset can require enormous computational effort, we suggest selecting a sample of observations and using this sampling information to achieve the inferential goal. Instead of the design-based survey sampling approach (which relates to the estimation of summary finite population measures) we consider the model-based sampling approach, which involves inference about parameters of a super-population model. This model is assumed to have generated the Big Dataset. Given a super-population model we can apply the theory of optimal design to draw a sample from the Big Dataset which contains the majority of information about the unknown parameters of interest.

Keywords:

Title: Effect of interim sample size recalculation on the distribution of the test statistic

Authors: Sergey Tarima and Nancy Fournoy

Affiliation: Medical College of Wisconsin and University of Missouri

Abstract:

Distribution theory of test statistics in the presence of sample size recalculation (SSR) is often considered under a fixed alternative hypothesis. At fixed alternatives, however, statistical power to reject the null hypothesis increases to one as sample size increases for any consistent test. This effectively eliminates the concept of statistical power from consideration whenever asymptotic distribution theory is used. To keep asymptotic power from diverging to one, statistical power against local alternative hypotheses is considered. An SSR changes the finite and large sample distributions of the test statistic. Finite and large sample distributions in the presence of SSR are found. Alternative

hypotheses converge to the null hypothesis at a SQRT(N) rate, where N is the sample size. Monte-Carlo simulation studies are used to evaluate distribution of test statistics under several hypothesized values of the treatment effect. Asymptotic distributions under blinded and unblinded sample size recalculation are considered.

Using SSR changes the single-sample (without SSR) distribution of test statistics. The conditional and unconditional distributions become mixture distributions. With few exceptions, the mixtures persist even asymptotically at both null and local alternatives. Consequently, Fisher information changes as well. If a single-sample test statistic follows a normal distribution, then with an SSR its finite and large sample distributions differ from normal. Previous research showed that estimation of nuisance parameters (such as standard deviation) in blinded SSR leads to an upward bias in total (re-estimated) sample size and this bias continues to affect the total sample size even asymptotically. This impact on the total sample size, however, does go away asymptotically under the local asymptotic framework which, in contrast to previous research, justifies the use of blinded SSR for large sample studies.

Impact of SSR on the distributions of test statistics and on Fisher information should not be ignored and needs to be accommodated when studies are being designed. In the presence of SSR, investigators should consider local asymptotic framework when characterizing large sample properties.

Title: Choosing Interim Sample Sizes in Group Sequential Designs
Authors: Nancy Fournoy and Sergey Tarima
Affiliation: University of Missouri and Medical College of Wisconsin
Abstract:
This work investigates sample sizes for interim analyses in group sequential designs. Traditional group sequential designs (GSD) rely on “information fraction” arguments to define the interim sample sizes. Then, interim maximum likelihood estimators (MLEs) are used to decide whether to stop early or continue the data collection until the next interim analysis. The possibility of early stopping changes the distribution of interim and final MLEs: possible interim decisions on trial stopping excludes some sample space elements. At each interim analysis the distribution of an interim MLE is a mixture of truncated and untruncated distributions. The distributional form of an MLE becomes more and more complicated with each additional interim analysis. Test statistics that are asymptotically normal without a possibly of early stopping, become mixtures of truncated normal distributions under local alternatives. Stage-specific information ratios are equivalent to sample size ratios for independent and identically distributed data. This equivalence is used to justify interim sample sizes in GSDs. Stage-specific information ratios derived from non-normally distributed data are more complicated than those derived from normally distributed data. Tarima and Flournoy [3] have proposed a new GSD where interim sample sizes are determined by a pre-defined sequence of ordered alternative hypotheses, and the calculation of information fractions is not needed. This innovation allows researchers to prescribe interim analyses based on desired power properties. In this manuscript we provide an example of the theory that is given in [3]. Here we compare interim power properties of a classical one-sided three stage Pocock design with a one-sided three stage design driven by maintaining constant power for three ordered alternatives at a pre-selected alpha-spending function
Keywords: adaptive clinical trials, large sample properties, interim analyses, hypotheses testing, statistical distributions, likelihood function

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Title: Operating characteristic guided design of group-sequential trials
Authors: Aniko Szabo
Affiliation: Medical College of Wisconsin
Abstract:

Group-sequential designs are commonly used for clinical trials to allow early stopping for efficacy or futility. While the design of a single-stage randomized trial is guided by a target power for an alternative hypothesis of interest, the addition of interim analyses is driven by technical choices that are less understandable for clinicians. For example, the commonly used Lan-DeMets methodology requires specification of the timing of analyses and error spending functions. Since the rationale and effect of these technical choices is often unclear, the operating characteristics of the final design are explored under various values of the parameter of interest, and the design is then adjusted until desired properties are obtained.

In this work we develop methods for constructing designs that achieve the desired operating characteristics without the need to specify error spending functions or the timing of analyses. Specifically, we consider designing a study for the mean difference δ of a normally distributed outcome with known variance. The null hypothesis $H0: \delta=\delta 0$ is tested versus $Ha: \delta=\delta A$, with power π at a significance level α. The interim analyses are designed so that for a pre-specified sequence δAk the study stops for efficacy at stage k with probability π if $\delta=\delta Ak$. If stopping for futility is also considered, then the requirement to stop for futility at stage k with probability πF if $\delta=\delta 0k$ for pre-specified sequence $\delta 0k$ can also be added.

We show that under some monotonicity restrictions, such designs exist for any choice of the timing of interim analyses. Specific designs can be selected by imposing additional optimality requirements, such as minimizing the expected sample size under the target alternative δA, or the average sample size under a weighted selection of the alternatives.

The utility of the proposed methods is demonstrated via a simulation study and illustrated examples of prior trials. The methods are implemented in the R package gsDesignOC.

Keywords: adaptive design, sequential design, interim analyses, hypotheses testing, ALPHA-spending functions