Scholar Poster Abstracts

Simultaneous Variable and Covariance Selection with the Multivariate Spike-and-Slab Lasso

Sameer Deshpande & Edward George (University of Pennsylvania) Veronika Rockova, (Booth School of Business, University of Chicago)

We propose a Bayesian procedure for simultaneous variable and covariance selection using continuous spike-and-slab priors in multivariate linear regression models where q possibly correlated responses are regressed onto p predictors. Rather than relying on a stochastic search through the high-dimensional model space, we develop an ECM algorithm similar to the EMVS procedure of Rockova & George (2014) targeting modal estimates of the matrix of regression coefficients and residual precision matrix. Varying the scale of the continuous spike densities facilitates dynamic posterior exploration and allows us to filter out negligible regression coefficients and partial covariances gradually. Our method is seen to substantially outperform regularization competitors on simulated data. We demonstrate our method with a re-examination of data from a recent observational study of the effect of playing high school football on several later-life cognitive, psychological, and socio-economic outcomes.

Type 1 Error and Power Considerations in Seamless Superiority/Non-Inferiority Clinical Trials

Ellen Gurary (Boston University)

We aim to identify methodology to maintain Type I error and power in a seamless trial designed to assess superiority of an experimental treatment vs. placebo and non-inferiority of the chosen experimental treatment vs. active control. We define a superiority/non-inferiority seamless trial as selecting the best experimental dose vs. placebo in Stage I; and assessing non-inferiority of that dose to active control, after adding subjects to yield adequate power, in Stage II. We simulate 10,000 trials consisting of three experimental doses, placebo, and an active control. We apply methodologies in Stage I, and test non- inferiority of the selected dose to the active control in Stage II. We assess type 1 error if inferiority exists and power if non- inferiority exists for various dose-response tends. We assess the need to adjust alpha in Stage II. Seamless superiority/non-inferiority trials are possible and could result in less development time and fewer subjects needed to assess efficacy than separate trials.

On The Mechanism Of Time-Trend Impact In Clinical Trials With Response Adaptive Randomization

Yunyun Jiang, Wenle Zhao & Valerie Durkalski (Medical University of South Carolina)

Clinical trial design and analysis often assume study population homogeneity. However, in trials with long recruitment periods, patient baseline profile and standard of care may evolve over time. This time-trend phenomenon may affect the treatment estimation and the trial operating characteristics, but have rarely been closely examined and reported in real studies. The goal of this research is to quantify the bias in the treatment estimation under different Bayesian response adaptive randomization (BRAR) algorithms and different time-trend patterns, so investigators can be better informed when designing a Bayesian adaptive trial and choose an appropriate RAR algorithm. The results demonstrate that in a BRAR designed trial, the type I error is inflated in the presence of a time trend, and the bias and drift in patients' allocation increases with the strength of allocation adaptation. The magnitude and direction of these changes vary by the time trend pattern. A potential model-based randomization algorithm is proposed that incorporates the time trend information to control for the type I error.

Cox Regression Model with Doubly Truncated Data

Lior Rennert (University of Pennsylvania)

Alzheimer's disease (AD) affects more than 5 million Americans, and this number is growing. In 2017 alone, AD and other dementias will have cost the nation an estimated $259 billion. Thus knowledge of factors affecting disease progression can greatly help reduce the burden of AD on society. However due to the inaccuracy of clinical diagnoses, many studies rely on autopsy-confirmed diagnoses of AD. These studies result in right truncation, since individuals who live past the end of the study are excluded from the sample since they do not receive a pathological diagnosis. Studies, which recruit subjects after the onset of AD, also result in left truncation, since individuals who succumb to AD before they enter the study are unobserved. Thus double truncation, the simultaneous presence of left and right truncation, is inherent in autopsy-confirmed AD studies. Ignoring this truncation scheme in the Cox model yields biased hazard ratio estimators. We propose a weighted estimating equation approach to adjust the Cox model in the presence of double truncation, which yields consistent and asymptotically normal estimators. We illustrate our approach on data from an autopsy-confirmed AD study.

Time Series Smoother For Effect Detection

Cheng You & Dennis K.J. Lin (Pennsylvania State University) C S. Stanley Young (CGStat)

In environmental epidemiology, it is often encountered that multiple time series data with a long-term trend, including seasonality, cannot be fully adjusted by the observed covariates. The long-term trend is difficult to separate from abnormal short-term signals of interest. This paper addresses how to estimate the long-term trend in order to recover short-term signals. Our case study demonstrates that the current spline smoothing methods can result in significant positive and negative cross-correlations from the same dataset, depending on how the smoothing parameters are chosen. To circumvent this dilemma, three classes of time series smoothers are proposed to detrend time series data. These smoothers do not require fine-tuning of parameters and can be applied to recover short-term signals. The properties of these smoothers are shown with both a case study using a factorial design and a simulation study using datasets generated from the original dataset. General guidelines are provided on how to discover short-term signals from time series with a long-term trend. The benefit of this research is that a problem is identified and characteristics of possible solutions are determined.

Registrant Poster Abstracts

Optimization of Oncology Combination Therapy by Integrating Multiple-layer Clinical Information

Xiaowei Guan (Pfizer)

In oncology, the challenges are many: while keeping patients safe with acceptable limits, the clinical trials should be small, adaptive and enable a quick declaration of the maximum tolerable dose (MTD) and /or recommended phase II dose (RP2D). Ideally, dose limiting events (DLTs) and responses (such as tumor reduction and pharmacodynamics (PD) endpoints) indicative of efficacy, as well as pharmacokinetic (PK) parameters should be considered in the dose escalation procedure, to balance clinical, statistical and operational aspects in a cost-effective way. Due to out of sync of DLT, PK and efficacy responses, challenges are posted on how to integrate different layers of clinical information quantitatively in a dual-agent setting. Optimization totality of all available clinical information plays an important role to key clinical study design elements such as schedule, escalation strategy, targeted patient population, etc. An outcome-adaptive Bayesian design by integrating multi-layer information is proposed to enable real-time adaption in the combination setting. It allows for more effective optimization based on totality of data to balance speed, reliability, efficacy and safety.

Statistical Challenges In Dose-Finding Early Phase Dual-Agent Oncology Studies

Nanshi Sha & Zhichao Sun (Boehringer Ingelheim)

With recent advance in scientific discoveries of pathophysiological process, such as the immuno-oncology pathways, more combination anti-cancer therapies are under investigations. The main objective of phase I oncology trial is typically to identify the maximum tolerated dose (MTD). Yet it is challenging to determine the optimal dose combination with acceptable toxicity profile for phase II development. Historically, 3+3 has been the conventional method in practice for decades. Recently modern dose escalations designs have been proposed including but not limited to Bayesian logistic regression model (BLRM), Partial ordering CRM (POCRM), Product of independent beta probabilities (PIPE), and 2- dimensional Biased Coin design, etc. In this poster, we outline the workflow process of BLRM and POCRM. To evaluate the operating characteristics, 3 hypothetical scenarios were set up with varying dose-toxicity relationships, based upon which simulations studies have been conducted. To compare the performance in terms of accuracy in identifying MTD, MTD selection and dose allocation were summarized as two metrics. To address safety concerns, number of patients with DLTs were also tabulated.

Methodologies of Correcting QT Interval from Heart Rate

Jiewei Zeng (Abbvie)

The QT-interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle, and it changes in an inverse relationship to heart rate. Therefore, to assess the pure QT effect of the drug on the subjects, QT intervals should be corrected for the heart interval or RR-interval. In general, there are three basic categories to adjust or correct the QT- interval for RR-interval, i.e, correction methods commonly used in medical practices, study-wide correction formulas derived from the data in the study, and individualized correction formulas derived for each individual in the study. This poster presents five different correction methods within each category and the application of each method on a simulated QT-RR dataset. The performance of each method will be assessed by the correlation coefficient between the adjusted QT- interval and RR-interval. Different ways of computing the correlation coefficient will also be discussed.