Equivalence of regression curves

Frank Bretz

Novartis Pharma AG, Switzerland

ABSTRACT

This talk investigates the problem whether the difference between two parametric models m_1, m_2 describing the relation between a response variable and several covariates in two non-overlapping populations is practically irrelevant, such that inference can be performed on the basis of the pooled sample. Statistical methodology is developed to test the hypotheses $H_0 : d(m_1, m_2) \geq \varepsilon$ versus $H_1 : d(m_1, m_2) < \varepsilon$ to demonstrate equivalence between the two regression curves m_1, m_2 for a pre-specified threshold ε, where d denotes a distance measuring the distance between m_1 and m_2. Our approach is based on the asymptotic properties of a suitable estimator $d(\hat{m}_1, \hat{m}_2)$ of this distance. In order to improve the approximation of the nominal level for small sample sizes a bootstrap test is developed, which addresses the specific form of the interval hypotheses. The results are illustrated by means of a simulation study and a data example.

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N-of-1 Trials for Individualized Patient Care

Yin Li[a], Weng Kee Wong[b], and K. C. Carriere[c]

[a]Ontario Medical Association, Canada
[b]University of California, Los Angeles, USA
[c]University of Alberta, Canada

ABSTRACT

This paper concerns statistical issues involving designs for patient-based medicine. In particular, it deals with a crossover design, a very popular design in clinical trials for comparing non-curative treatments for their efficacy. Typically, designs were constructed to optimize the average subjects and not ideal in clinical and medical applications. N-of-1 trials are randomized multi-crossover experiments using two or more treatments on a single patient. They provide evidence and information on an individual patient, thus optimizing the management of the individual's chronic illness. We build a single and aggregated N-of-1 universally optimal designs to accommodate both individual and average patients. We also construct optimal N-of-1 designs for two treatments.

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Design and Analysis of Sequential Multiple-Assignment Randomized Trials (SMARTs)

Bibhas Chakraborty

Duke-NUS Medical School, Singapore

ABSTRACT

Management of chronic health conditions requires ongoing medical interventions, e.g., a sequence of treatments. However, traditional randomized controlled trials (RCTs) were developed to compare stand-alone treatments rather than treatment sequences. This discrepancy between clinical practice and clinical trials is largely addressed by the modern framework of sequential multiple-assignment randomized trial (SMART) design. These designs not only allow comparison of embedded treatment sequences, but also facilitates discovery of optimal personalized treatment allocation rules sometimes referred to as dynamic treatment regimes. In this talk, we will discuss various key features of the SMART design, various contexts where they can be used, and a variety of data analysis approaches associated with such designs. The methodological concepts will be illustrated through several real trial examples.

Optimal linear combination of biomarkers for multi-category diagnosis

Yi-Hau Chen

Institute of Statistical Science Academia Sinica, Taiwan

ABSTRACT

The receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) have been popularly employed in evaluating the diagnosis accuracy for diseases with binary outcome categories, and have been naturally used as the utility measures for finding the "optimal" linear combination of multiple biomarkers, in the hope to improve the diagnostic accuracy based on each single biomarker. For diseases with more than two outcome categories, the ROC surface and the volume under the ROC surface (VUS), or the ROC manifold and the hypervolume under the ROC manifold (HUM), have been analogously proposed as diagnostic accuracy measures. However, finding optimal combinations of biomarkers based on the HUM criterion is less easily feasible in computation, especially when the number of disease categories is more than three and the number of biomarkers is large. In this study, we propose two new indices for evaluating the diagnostic accuracy for multi-category diagnosis, which are related to the lower and upper bounds of HUM, and involve only diagnostic accuracies for comparing adjacent pairs of outcome categories. We then propose finding the optimal linear combinations of biomarkers for multi-category diagnosis using the new indices as the criterion functions. Simulations and real data examples show that the optimal linear combinations identified by the new proposal perform quite well in diagnostic accuracy, and can be much more efficient in computation than the HUM-based method. (Joint work with Dr. Man-Jen Hsu)

Sequential Designs for Individualized Dosing Algorithms

YING KUEN (KEN) CHEUNG

Columbia University, USA

ABSTRACT

This talk addresses dose finding in clinical trials where individuals exhibit biologic characteristics that alter the toxicity risks of the individuals. In these situations, instead of determining a dose that works for every patient, the trial aims to identify a dosing algorithm that prescribes dose according to the patient's biomarker or pharmacokinetic expression. Specifically, we aim to dose patients around a pre-specified level of area under the curve of irinotecan concentration using the patients' baseline phenotypes that predict drug clearance. We propose least squares recursion procedures to estimate the dosing algorithm sequentially with an aim to treat patients in the trial around the true unknown dosing algorithm, and introduce a novel application of classical eigenvalue theory that guarantees convergence to the true dosing algorithms. Our simulation study demonstrates that using an eigenvalue constraint improves the efficiency of the recursion by as large as 40 per cent, while concentrating in-trial patient allocation around the true dosing algorithm. We also provide practical guidance on design calibration, and design future irinotecan studies based on data from our first trial.

Optimal designs for comparing (dose response) curves

HOLGER DETTE

Ruhr-Universität Bochum

ABSTRACT

We consider the optimal design problem for a comparison of two regression curves, which is used to establish the similarity between the dose response relationships of two groups. An optimal pair of designs minimizes the width of the confidence band for the difference between the two regression functions. Optimal design theory (equivalence theorems, efficiency bounds) is developed for this non standard design problem and for some commonly used dose response models optimal designs are found explicitly. The results are illustrated in several examples modeling dose response relationships. It is demonstrated that the optimal pair of designs for the comparison of the regression curves is **not** the pair of the optimal designs for the individual models. In particular it is shown that the use of the optimal designs proposed in this paper instead of commonly used "non-optimal" designs yields a reduction of the width of the confidence band by more than 50%.

Multiplicity considerations in design, data monitoring and analysis of clinical trials with co-primary endpoints

Toshimitsu Hamasaki[a], Scott R. Evans[b], Koko Asakura[a], and Tomoyuki Sugimoto[c]

[a]National Cerebral and Cardiovascular Center, Japan
[b]Harvard T.H. Chan School of Public Heath, USA
[c]Kagoshima University, Japan

ABSTRACT

In clinical trials, most commonly, a single outcome is selected as a primary endpoint and then used as the basis for the trial design including sample size determination, interim data monitoring, final analyses, and reporting and publication of results. However, many recent clinical trials have utilized more than one primary endpoint as co-primary. "Co-primary" means that a trial is designed to evaluate whether a test intervention has an effect on all of the primary endpoints. Failure to demonstrate an effect on any single endpoint implies that the beneficial effect to the control intervention cannot be concluded. The rationale for this is that the use of a single endpoint may not provide a comprehensive picture of the intervention's multidimensional effects. The resulting need for new approaches to the design and analysis of clinical trials with multiple co-primary endpoints has been noted. When designing the trial to evaluate the joint effects on all of the endpoints, no adjustment is needed to control the Type I error rate. The hypothesis associated with each endpoint can be evaluated at the same significance level that is desired for demonstrating effects on all of the endpoints. However, the Type II error rate increases as the number of endpoints to be evaluated increases. This is referred to as "multiple co-primary endpoints". In contrast, when designing the trial to evaluate an effect on at least one of the endpoints, an adjustment is needed to control the Type I error rate. This is referred to as "multiple primary endpoints". In this presentation, we provide an overview of the design, data monitoring, and analyses of clinical trials with multiple co-primary endpoints. We review recently developed methods for fixed-sample and group-sequential settings. We discuss practical considerations and provide guidance for the application of these methods.

Entropy Learning for Dynamic Treatment Regimes

Jialiang Li

National University of Singapore

ABSTRACT

Estimating optimal individualized treatment rules (ITRs) in single- or multi-stage clinical trials is one key solution to personalized medicine and has received more and more attention in statistical community. Recent development suggests that using machine learning approaches can significantly improve the estimation over model-based methods. However, proper inference for the estimated ITRs has not been well established in machine learning based approaches. In this paper, we propose an entropy learning approach to estimate the optimal individualized treatment rules (ITRs). We obtain the asymptotic distributions for the estimated rules so further provide valid inference. The proposed approach is demonstrated to perform well in finite sample through extensive simulation studies. Finally, we analyze data from a multi-stage clinical trial for depression patients. Our results offer novel findings that are otherwise not revealed with existing approaches.

Analysis of Massive Genome, Exposome and Phenome Data

XIHONG LIN

Harvard University, USA

ABSTRACT

Massive 'ome data, including genome, exposome, and phenome data, are becoming available at an increasing rate with no apparent end in sight. Examples include Whole Genome Sequencing data, smartphone data, and Electronic Medical Records. For example, Whole Genome Sequencing data and different types of genomic data have become rapidly available. Two large ongoing whole genome sequencing programs (Genome Sequencing Program (GSP) of National Human Genome Research Institute and Trans-omics for Precision Medicine Program (TOPMed) of the National Heart, Lung and Blood Institute) plan to sequence 300,000-350,000 whole genomes. These massive genetic and genomic data, as well as exposure and phenotype data, present many exciting opportunities as well as challenges in data analysis and result interpretation. In this talk, I will discuss analysis strategies for some of these challenges, including rare variant analysis of whole-genome sequencing association studies, and integrative analysis of different types of genetic and genomic, environmental data using causal mediation analysis.

Sequential Multiple Assignment Randomization Trials with Enrichment Design

YING LIU[a], YUANJIA WANG[b], AND DONGLIN ZENG[c]

[a]*Medical College of Wisconsin, USA*
[b]*Columbia University, USA*
[c]*University of North Carolina at Chapel Hill, USA*

ABSTRACT

Sequential multiple assignment randomization trial (SMART) is a powerful design to study Dynamic Treatment Regimes (DTRs) and allows causal comparisons of DTRs. To handle practical challenges of SMART, we propose a SMART with Enrichment (SMARTER) design, which performs stage-wise enrichment for SMART. SMARTER can improve design efficiency, shorten the recruitment period, and partially reduce trial duration to make SMART more practical with limited time and resource. One extreme case of the SMARTER is to synthesize separate independent single-stage randomized trials with patients who have received previous stage treatments. We show data from SMARTER allows for unbiased estimation of DTRs as SMART does under certain assumptions. Furthermore, we show analytically that the efficiency gain of the new design over SMART can be significant especially when the dropout rate is high. Lastly, extensive simulation studies are performed to demonstrate performance of SMARTER design, and sample size estimation in a scenario informed by real data from a SMART study is presented.

Designs of Dose Escalation Studies in Phase I Oncology Trials

YING LU

Stanford University, USA

ABSTRACT

In this talk, I will review curve-free Bayesian decision models using monotonicity of dose-toxicity curve in selection of MTD for single and combined drugs. I will then discuss the limitations of MTD in finding the proper cancer treatment. We explore a new approach to joint model the drug activity related to efficacy and safety a dose window that is safe and has desired biological activity level. We demonstrate our methods through simulations.

Adaptive Biomarker Trial Designs

Adrian Mander

MRC Biostatistics Unit, UK

ABSTRACT

Response to treatments is often highly heterogeneous. Increasing availability of biomarkers and targeted treatments has led to the need for trial designs that efficiently test new treatments in biomarker-stratified patient subgroups. Often new treatments are targeted at a specific biomarker subgroup, but may in fact work in a narrower or broader set of patients.

I will initially discuss an optimal version of the two-stage single-arm adaptive enrichment design, proposed by Jones and Holmgren [1]. Within this design there is an interim analysis to check for futility in the whole trial population and allows the potential to only recruit in a biomarker subgroup after this analysis. This approach gives rise to additional error probabilities that need to be considered. As this design uses exact binomial calculations searching the design space for the best designs is computationally intense and billions of potential designs were evaluated to find the ones with the best operating characteristics [2].

I will then go on to describe Bayesian adaptive methodology for trials that have multiple treatments and biomarkers. The proposed design incorporates biological hypotheses about the links between treatments and biomarker subgroups, but allows alternative links to be formed during the trial. The statistical properties of the method compare well to alternative designs available. This design has been developed for trials in ovarian cancer and breast cancer and some methodology issues specific to each application will be discussed. These include the use of continuous biomarker information to allocate patients and adding in new treatments and biomarkers during the trial [3].

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A Nonparametric Bayesian Basket Trial Design

PETER MÜLLER[a], YANXUN XU[b], APOSTOLIA M. TSIMERIDOU[c], AND DON BERRY[c]

[a]*UT Austin, USA*
[b]*Johns Hopkins University, USA*
[c]*M.D. Anderson Cancer Center, USA*

ABSTRACT

Targeted therapies on the basis of genomic aberrations analysis of the tumor have become a mainstream direction of cancer prognosis and treatment. Regardless of tumor type, trials that match patients to targeted therapies for their particular genomic aberrations, have become a mainstream direction of therapeutic management of patients with cancer. Therefore, finding the subpopulation of patients who can most benefit from an aberration-specific targeted therapy across multiple cancer types is important. We propose an adaptive Bayesian clinical trial design for patient allocation and subpopulation identification. We start with a decision theoretic approach, including a utility function and a probability model across all possible subpopulation models. The main features of the proposed design and population finding methods are that we allow for variable sets of covariates to be recorded by different patients, adjust for missing data, allow high order interactions of covariates, and the adaptive allocation of each patient to treatment arms using the posterior predictive probability of which arm is best for each patient. The new method is demonstrated via extensive simulation studies.

Personalised medicine : from hype to scepticism to realism?

STEPHEN SENN

Luxembourg Institute of Health, Luxembourg

ABSTRACT

For at least twenty years now, we have been promised that a personalised medicine revolution is just around the corner. Despite some notable successes, such progress as there has been is far from constituting a revolution. I present some reasons for thinking that naive approaches to analysing clinical trials may have led to the scope for personalised medicine being vastly overrated. In the first part of this lecture I shall try explain, from the statistical point of view, what has gone wrong, with extravagant causal interpretations of arbitrary responder dichotomies being a major culprit.

The fact, however, that progress has been slow does not mean the goal is not worth pursuing where the opportunity presents itself. Identifying that opportunity, however, is not easy. In the second part of the lecture I shall consider some of the possibilities, paying particular attention to careful analysis of components of variation and designs that permit this. For chronic diseases, n-of-1 trials seem particularly suitable although, given suitable models and plausible assumptions, repeated measures designs may offer an alternative. There may also be further opportunities in translating general clinical findings into personal medical decisions.

I conclude that the most important task for drug development remains finding drugs that work well on average but that on occasion the goal of personalising will be worthwhile. However, to help realise this, statisticians need to pay attention to the statistical challenges.

Learning VA Healthcare System Through Large Cooperative Studies

MEI-CHIUNG SHIH[1], YING LU[1], RYAN FERGUSON[2], AND GRANT HUANG[3]

[1] *VA Palo Alto Health Care System and Stanford University, USA*
[2] *VA Boston Health Care System and Boston University, USA*
[3] *Office of Research and Development, Department of Veterans Affairs, USA*

ABSTRACT

The VA Cooperative Studies Program (CSP) is a division in the Office of Research and Development in the US Department of Veterans Affairs (VA). CSP has 44-years history of planning and conducting large multicenter clinical trials and epidemiological studies initiated by VA investigators within the VA Healthcare System. The mission of CSP is to advance the health and care of Veterans through cooperative research studies that produce innovative and effective solutions to Veteran and national healthcare problems. In this talk, we provide an overview of CSP and examples of our innovations to integrate large clinical trials/observational studies with the largest national healthcare system. We will also discuss innovative clinical trial designs and statistical challenges in learning healthcare system: (a) comparative effectiveness research on approved treatments and treatment strategies, (b) sequential multiple adaptive randomization for dynamic treatment strategies, and (c) stage-wise designs of large pragmatic trials.

Adaptive Enrichment Trials for Biomarker-guided Treatments

NOAH SIMON[a] AND RICHARD SIMON[b]

[a]*University of Washington USA*
[b]*National Cancer Institute, USA*

ABSTRACT

The biomedical field has recently focused on developing targeted therapies, designed to be effective in only some subset of the population with a given disease. However, for many new treatments, characterizing this subset has been a challenge. Often, at the start of large-scale trials the subset is only rudimentarily understood. This leads practitioners to either 1) run an all-comers trial without use of the biomarker or 2) use a poorly characterized biomarker that may miss parts of the true target population and potentially incorrectly indicate a drug from a successful trial.

In this talk we will discuss a class of adaptive enrichment designs: clinical trial designs that allow the simultaneous construction and use of a biomarker, during an ongoing trial, to adaptively enrich the enrolled population. For poorly characterized biomarkers, these trials can significantly improve power while still controlling type one error. However there are additional challenges in this framework: How do we adapt our enrollment criteria in an "optimal" way? (what are we trying to optimize for?) How do we run a formal statistical test after updating our enrollment criteria? How do we estimate an unbiased treatment effect-size in our "selected population"? (combatting a potential selection bias) In this talk we will give an overview of a class of clinical trial designs and tools that address these questions.

The promise and peril of healthcare analytics: two examples in healthcare resource planning and frequent flyer identification

Yik-Ying Teo

National University of Singapore

ABSTRACT

There has been a lot of hype around the application of data science and analytical approaches in health and healthcare research. In my talk, I will use two specific examples to highlight the potential and danger of adopting an analytic approach. Firstly, I will discuss how the use of retrospective operational data can be used for building resilience in the health system through careful allocation of limited healthcare resources. In my second example, I will describe how the naĂŻve application of predictive analytics in healthcare may not yield the anticipated results when the medical context is not well-understood.

Methods on the usage of common controls for genetic association studies

CHAOLONG WANG

*Genome Institute of Singapore, A*STAR*

ABSTRACT

The increasing amount of genetic data generated by sequencing and array genotyping experiments has led to new opportunities for discoveries in genetic disease studies. In particular, leveraging public data as "common controls" in disease association studies is an appealing strategy to increase statistical power. Such study design need to be treated carefully due to potential confounders such as batch effects due to sequencing depth, population structure, and cryptic relatedness. I will present two methods that we are developing to help control for these confounding factors. The first method, SEEKIN, can infer relatedness between pairs of individuals using sparse sequencing reads from off-target regions in target sequencing experiments. We demonstrate a statistical model of genotype uncertainty associated with shallow sequencing data. By properly modeling the uncertainty, we can obtain the kinship coefficient between two individuals as good as using high-quality array genotyping data, enabling control of family relatedness and estimation of trait heritability in target sequencing studies. The second method, CLR-SKAT, is a novel rare variant association test for matched case-control samples. Ancestry matching can be used to avoid spurious association signals due to population structure. We show that conventional association tests, when applied to matched case-control data, have uncontrolled type 1 error rate. Our proposed method based on conditional logistic regression (CLR) is the only test that controls type 1 error rate in all simulation scenarios and has the highest statistical power. Our methods provide the basis for future research to control for batch effects in joint analysis of different datasets and to leverage large common control datasets to empower disease association studies.

A Brief Overview of Adaptive Enrichment with Subpopulation Selection in Precision Medicine*

Sue-Jang Wang

U.S. Food and Drug Administration, USA

ABSTRACT

According to the National Research Council, personalized medicine is an older term with a meaning similar to precision medicine. In this presentation, several other terms used in the literature, e.g., individualization of medical treatment, stratified medicines, pharmacogenomics, etc., may also be referred. Many statistical approaches on adaptive enrichment with subpopulation selection have been proposed in the literature that facilitate early discoveries and translate exploratory observations to form the basis for confirmatory evidence setting. In recent years, we are seeing methodological advances not only for confirmatory studies, but, also for exploratory studies. A brief overview of statistical designs, analyses, and issues with literature examples where appropriate will be given. The presentation theme will focus on study designs, statistical analytical considerations and issues that can facilitate identification of effective treatments based on a patient's intrinsic molecular genomics/genetics profile and/or baseline characteristics.

Matched Learning for Estimating Optimal Individualized Treatment Rules from Clinical Trials and Observational Studies

Yuanjia Wang

Columbia University, USA

ABSTRACT

Individualized treatment rules (ITRs) tailor medical treatments according to individual-specific characteristics. They are gradually being considered to replace "one-size-fits-all" strategy to personalize medical decision making. In this paper, we propose a machine learning approach to estimate ITR, referred as matched learning (M-Learning), which is applicable to both observational studies and randomized controlled trial (RCT). M-learning proposes to perform matching instead of inverse probability weighting (as in many existing methods for estimating ITR) to more accurately estimate individual response under alternative treatments and alleviate confounding in observational studies. A matching function is proposed to compare outcomes for matched pairs where various types of outcomes (including continuous, ordinal and discrete responses) can easily be accommodated. We further improve efficiency of estimating ITR by augmentation and double robust matching. The advantage of M-learning includes improved accuracy, robustness, and flexibility to accommodate complex patterns among features collected in observational studies. We prove Fisher consistency of M-learning and conduct extensive simulation studies of RCT and observational studies. We show that M-Learning outperforms existing methods (e.g., outcome weighted learning or Q-learning) when propensity scores are misspecified and in certain scenarios of presence of unmeasured confounders. Lastly, we apply our method to an RCT on anorexia nervosa patients and a study of optimal second-line treatments for type 2 diabetes (T2D) patients using electronic health records (EHR).

NOC: Nonparametric Overdose Control in Phase I Clinical Trials

Guosheng Yin

The University of Hong Kong, Hong Kong

ABSTRACT

Under the framework of Bayesian model selection, we propose a nonparametric overdose control (NOC) design for dose finding in phase I clinical trials. Each dose assignment is guided via a feasibility bound, which thereby can control the number of patients allocated to excessively toxic dose levels. We further develop a fractional NOC (fNOC) design in conjunction with a so-called fractional imputation approach, to account for late-onset toxicity outcomes. Extensive simulation studies have been conducted to show that both the NOC and fNOC designs have robust and satisfactory finite-sample performance compared with the existing dose finding designs. The proposed methods also possess several desirable properties: treating patients more safely and also neutralizing the aggressive escalation to overly toxic doses when the toxicity outcomes are late-onset. With the emergence of novel targeted anti-cancer agents, drug combinations have been recognized as cutting-edge development in oncology. However, limited attention has been paid to the overdose control in the existing drug-combination dose-finding trials. We develop the multi-agent nonparametric overdose control (MANOC) design for dose finding in phase I drug-combination trials. Based on a Bayesian decision-theoretic approach, we control the probability of overdosing in a local region at the current dose combination. While the MANOC can prevent patients from being allocated to over-toxic dose levels, its accuracy and efficiency are still competitive to the existing designs.

BOIN: a novel platform for designing early phase single-agent and drug-combination clinical trials

YING YUAN[a] AND MARK GILBERT[b]

[c]*University of Texas MD Anderson Cancer Center, Houston, USA*
[b]*National Cancer Institute, Bethesda, USA*

ABSTRACT

We introduce Bayesian optimal interval (BOIN) designs as a novel platform for designing early phase single-agent and drug-combination clinical trials [1, 2, 3]. The BOIN design is motivated by the top priority and concern of clinicians, which is to effectively treat patients and minimize the chance of exposing them to subtherapeutic or overly toxic doses. The BOIN design is easy to implement in a way similar to algorithm-based designs, such as the 3+3 design, but is more flexible for choosing the target toxicity rate and cohort size and yields a substantially better performance that is comparable to that of more complex model-based designs. The BOIN design can handle both single-agent and drug-combination phase I trials, and be used to find a single or multiple maximum tolerated doses (MTD). The BOIN design has desirable statistical properties of being coherent and consistent. Web applications with intuitive graphical user interface are freely available at www.trialdesign.org.

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