Opportunities of Statistics for Precision Medicine in Drug Development

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ABSTRACT

The overarching mission of the pharmaceutical industry is to develop medical products that can improve human health. Scientific discoveries and innovations in research and development are very critical in the success of developing new medical products such as drugs, vaccines, and medical devices. Working closely with scientists and clinical researchers, statisticians play a key role in solving real problems in the drug development process, from basic discovery to clinical trials and post marketing surveillance. In this presentation we will provide some perspectives and opportunities for precision medicine in drug development from statistical perspectives. We will discuss how statistics and analytics can be utilized to detect signals and analyze biomarker data from discovery to clinical trials. For example, machine learning methods are used to identify subgroups of patients that are more likely to benefit from the medical treatment. Statistical analytic methods can be used to develop biomarkers that can enrich the clinical trial design. Finally, examples will be used to illustrate the utility of some of these methods.

Depth Regression with Application to Functional Data

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ABSTRACT

We consider a regression setup, where the response is multivariate and the covariate is a random element in a metric space. This setup includes multivariate regression with functional covariate as a special case. We develop a regression method based on statistical depth functions in this setup. This depth based regression yields information about the centre as well as other parts of the conditional distribution of the response given the covariate. We construct conditional central regions based on depth, which yield measures of conditional spread and skewness. A test for heteroscedasticity is developed based on the measure of conditional spread. The usefulness of our methodology is demonstrated in simulated and real datasets. The consistency of sample conditional central regions and the resulting measures of conditional spread and skewness is established.

Biomarker-based subgroup selection for treatment assignment

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ABSTRACT

Precision medicine applies molecular technologies and statistical methods to identify biomarkers that indicate differential disease outcomes or treatment responses for better matching of disease with specific therapies to optimize treatment assignment. The success of precision medicine lies in the development of biomarker-based Subgroup Selection Procedures to identify the right patients for the right treatment and vice versa. This presentation will cover the three steps to develop a Subgroup Selection Procedure: 1) Biomarker Identification, 2) Subgroup Selection, and 3) Subgroup Analysis to assess clinical utility. Biomarker Identification involves fitting regression models to identify a set of potential prognostic and/or predictive biomarkers from the measured genomic variables. Subgroup Selection develops a prediction model based on the biomarkers identified to partition patients into subgroups that are homogeneous with respect to outcomes of the disease and/or responses to a specific treatment. Subgroup Analysis evaluates accuracy of patient treatment assignment and assesses enhancement of treatment efficacy. Procedures are illustrated by simulations and analyses of cancer datasets. Statistical issues and challenges will be briefly discussed, including identification of prognostic and predictive biomarkers, false and true positives in biomarker identification respect to predictive model development, class-imbalanced prediction, safety biomarkers for drug-induced toxicity, subgroup domain and clinical target variable.

Multiplicity issues in exploratory subgroup analysis

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ABSTRACT

The general topic of biomarker discovery and subgroup identification has attracted much attention in the clinical trial literature due to its important role in the development of tailored therapies and personalized medicine. Subgroup search methods are commonly used in late-phase clinical trials to identify subsets of the trial population with desirable characteristics such as enhanced efficacy or acceptable safety. Historically, post-hoc or exploratory subgroup exploration has been criticized for being extremely unreliable. To address this well-justified criticism, principled approaches to exploratory subgroup analysis based on recent advances in machine learning and data mining have been developed. These approaches treat subgroup investigation as a special case of model selection and emphasize fundamental statistical principles, including the importance of performing multiplicity adjustments to account to selection bias inherent in subgroup search. For a comprehensive review of principled approaches to subgroup identification in clinical trials with a discussion of resampling-based adjustments, see Lipkovich, Dmitrienko and D'Agostino [6]. The benefits of explicitly addressing multiplicity issues in exploratory subgroup analysis have been demonstrated in multiple clinical trial applications, see, for example, [5, 2]. This talk will focus on multiplicity issues arising in exploratory subgroup analysis [1] and on resampling-based procedures that provide weak control of the probability of incorrect subgroup discovery. Multiplicity corrections in the context of principled subgroup search will be illustrated using the SIDES (subgroup identification based on differential effect search) method [3] as well as the SIDEScreen method [4] which extends the original SIDES methodology by incorporating an efficient biomarker screen. A case study based on a Phase III trial will be presented to discuss the details of subgroup search algorithms with resampling-based multiplicity adjustment procedures.

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Bayesian Adaptive Designs in the Era of Personalized Medicine–Promise and Progress

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ABSTRACT

Clinical trial is a prescribed learning process for identifying safe and effective treatments. In recent years, rapid advancements in cancer biology, immunology, genomics, and treatment development demand innovative methods to identify better therapies for the most appropriate population in a timely, efficient, accurate, and cost-effective way. In my talk, I will first illustrate the concept of Bayesian update and Bayesian inference, a superior alternative to the traditional frequentist approach. Bayesian methods take the "learn as we go" approach and are innately suitable for clinical trials [1]. Then, I will give an overview of Bayesian adaptive designs in the areas of adaptive dose finding, posterior and predictive probability calculations, outcome adaptive randomization, multi-arm platform design [2], and hierarchical modeling, etc. Finally, real applications including BATTLE trials [3] in lung cancer and I-SPY trials in breast cancer will be given. Bayesian adaptive clinical trial designs increase the study efficiency, allow more flexible trial conduct, and treat more patients with more effective treatments in the trial but also possess desirable frequentist properties. Perspectives will be given on translating theory to practice to enhance the clinical trial success and speed up drug approval. We have developed Shiny applications and other software tools to assist the learning and implementation of Bayesian adaptive designs such that we can turn promise into progress. Many useful software can be found at the followings two sites.
https://biostatistics.mdanderson.org/softwareOnline/
https://biostatistics.mdanderson.org/softwareDownload/

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Integrative Analysis for Incorporating the Microbiome to Improve Precision Medicine

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ABSTRACT

The gut microbiome impacts health and risk of disease by dynamically integrating signals from the host and its environment. High throughput sequencing technologies enable individualized characterization of the microbiome composition and function. The resulting data can potentially be used for personalized diagnostic assessment, risk stratification, disease prevention and treatment. In this talk, I will present several ongoing microbiome studies at the University of Pennsylvania and provide some empirical evidence of using microbiome in precision medicine. I will talk about some statistical issues related to species abundance quantification, compositional data regression and compositional mediation analysis.

Classification with Ultrahigh-Dimensional Features

Yi Li

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ABSTRACT

In ultrahigh-dimensional classification, using all features leads to poor performance. It is important to select a subset of important features to address the impact of dimensionality on classification. Most current ultrahigh-dimensional screening methods assume an independence rule, which is too restrictive for analyzing the "omic"data. In this paper, we introduce a novel and computationally efficient multivariate screening and classification method for ultrahigh-dimensional data. Leveraging inter-feature correlations, the proposed method enables detection of marginally weak and sparse signals and recovery of the true informative feature set, and achieves optimal misclassification rates asymptotically. We show that the proposed procedure provides more powerful discovery and classification boundaries. The performance of the proposed procedure is evaluated using simulation studies and an application of classifying post-transplantation rejection types based on genome-wide microarray probes.

A regression tree method for subgroup identification of differential treatment effects

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ABSTRACT

In the fight against modern diseases, such as cancer, it is often difficult to discover treatments that benefit all patients. Therefore it is important to identify subgroups of patients for whom the treatment has an above-average effect. Regression trees are natural for this task because they partition the data space using patient characteristics. The talk focuses on an algorithm called GUIDE, which is free of biases in variable selection and is applicable to randomized trials with two or more treatment arms, to censored, multiple and longitudinal responses, and to predictor variables with missing values. A bootstrap technique for constructing confidence intervals of the treatment effects is used for post-selection inference.

Optimizing personalized treatment in dose ranging study

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ABSTRACT

We consider the problem of predicting the personalized minimum effective dose and estimating the dose-dependent optimal subgroups in dose-ranging studies. Our research is motivated by a real randomized, double-blind, placebo-controlled phase II dose-ranging study with genetic markers. One goal of the analysis is to identify subgroups with enhanced benefit/risk profiles with appropriate doses and inform the study design of future phase III trials. To the best of our knowledge, this problem has not been systematically studied before. We proposed a novel framework to nonparametrically model the dose-dependent biomarker-outcome relationship and to estimate the personalized effective dose and dose-dependent optimal subgroups. Our proposed method will be useful for identifying the respondent subgroups and their accompanying doses for the future study design. We illustrate the proposed method with simulation studies. Our method compares favorably to two ad-hoc approaches.

Multi-loci association test in genetic association study using similarity between individuals

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ABSTRACT

The common paradigm in genome wide association studies (GWAS) is to test for association using only one SNP at a time that gives rise to multiple comparison problems ignoring their genomic and environmental context. Gene-based association tests are gaining importance for the analysis of genome-wide association studies (GWAS) because it reduces multiple testing burdens and also provides directions for future functional studies. Moreover, with whole-genome sequencing on the horizon, there is increasing recognition that agnostic biostatistical approaches will get us no far, development of comprehensive and fully informative analyses of GWAS using newer approaches is required that combine information from multiple markers at a time. So, within a gene or any genomic region of interest, testing for joint association of genetic variants would be desirable to determine their synergistic effects. Based on this idea we have proposed kernel based association test (KBAT) for binary trait as well as for quantitative phenotype (QT-KBAT) including information for both common and rare variants. These tests are shown to be powerful to detect such association. We have evaluated the power of the proposed test statistics for case-control samples and quantitative traits using the extensive simulated data sets. We have also extended our multi-loci approach to family data and also to study gene-gene interaction. In each case, we have developed asymptotic distribution of the test statistic under null hypothesis of no association. This enables us to calculate p-value vary fast without using any time consuming computational procedure.

The utility of adaptive enrichment designs in the era of developing personalized medicine

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ABSTRACT

Drug development field has been evolving from empirical medicine to precision or personalized medicine. Recent development of statistical methods and their companion software have enabled structured search of sub-population that might have an enhanced treatment effect in controlled clinical trials. Challenges remain as to how to construct a clinical program that can efficiently develop the compound with an initially identified but not yet confirmed sub-population that potentially benefit from the treatment. In this presentation, we first share our general practice in subgroup identification in early phase clinical trials and the challenges that we often face after obtaining the evidence that suggest the existence of a clinically meaningful sub-population. The questions at stake are how to create the clinical program moving forward with good speed and high probability of success given several important unknowns at hand. We then propose considering adaptive enrichment designs using predictive enrichment strategy [1] to allow learning and confirming of the subpopulation in one same study to address the challenges. To illustrate such proposal, we present the ideas and general design algorithm for a Bayesian adaptive subgroup-identification enrichment design [2]. This design uses patients' biomarker profile and clinical outcome to continuously partition the covariate space in a Bayesian framework in searching for the sub-population of enhanced treatment effect. When the pre-specified criterion of adaptation is met, the design triggers modification of study entry criteria to allow focused learning about the sub-population and ascertain its definition. In the second stage of the study, new sample size and different dose groups can also be considered to ensure collection of sufficient evidence to inform late phase development.

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Individualized Multi-directional Variable Selection

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ABSTRACT

In this talk, we propose an individualized variable selection approach to select different relevant variables for different individuals. In contrast to conventional model selection methods, the key component of the new approach is to construct a separation penalty with multi-directional shrinkages including zero, which helps enable individualized modeling to distinguish strong signals from noise. As a byproduct, the proposed model identifies subgroups among which the individuals share similar effects, and thus improves estimation efficiency and personalized prediction accuracy. Another advantage of the proposed model is that it can incorporate within-subject correlation for longitudinal data. We provide a general theoretical foundation in double-divergence modeling where the number of subjects and the number of within-subject measurements both go to infinity, and therefore yield high-dimensional individual parameters. In addition, we present the oracle property for the proposed estimator to ensure its optimal large sample property. Simulation studies and an application to HIV longitudinal data are illustrated to compare the new approach to existing penalization methods.

Subgroup Identification for Personalized Medicine

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ABSTRACT

The topic of personalized medicine has garnered increasing amount of attention in recent years, a trend that is expected to continue given the demand for both improved outcome and efficiency by patients and healthcare providers. One of the most important contributions to this effort by the pharmaceutical industry is the development of what is often referred to as tailored therapies. During drug development, it is often desirable and sometimes crucial to identify, based on data collected from randomized clinical trials, subgroup of patients defined by biomarkers who are expected to have an enhanced response to an investigational treatment. This effort has been made more feasible by recent advances in statistical methods for effective identification of such patient subgroups. In this talk, I will review some of these methods; furthermore, I will present approaches to evaluate subgroup identification methods and optimize the analysis in any given application, thereby improving the various key aspects of subgroup identification, namely maximized power to identify relevant subgroups and improved quality of the subgroups identified, while still adequately controlling the type I error rate.

Accounting for Selection Bias in High-Throughput Experiments

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ABSTRACT

With recent advances in high throughput technology, researchers often find themselves running a large number of hypothesis tests (thousands+) and estimating a large number of effect-sizes. Generally there is particular interest in those effects estimated to be most extreme. Unfortunately naive estimates of these effect-sizes (even after potentially accounting for multiplicity in a testing procedure) can be severely biased. In this talk we explore this bias from a frequentist perspective. We show that were the bias known apriori one could build estimates that (potentially significantly) dominate our usual estimators. In practice the bias will be unknown — we discuss a bootstrap procedure to estimate it. Unlike other proposals for debiasing estimates, our procedure implicitly adjusts for unknown dependence between the features. Finally, we empirically demonstrate the efficacy of our approach and relate it to ideas in empirical Bayes.

Random Forests of Interaction Trees for Estimating Individualized Treatment Effects in Randomized Trials

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ABSTRACT

Assessing heterogeneous treatment effects has become a growing interest in advancing stratified/personalized medicine. Individualized treatment effects (ITE) play a critical role in such an endeavor. Concerning experimental data collected from randomized trials, we put forward an ensemble learning method, termed random forests of interaction trees (RFIT), for estimating ITE on the basis of interaction trees [1]. To this end, we first propose a smooth sigmoid surrogate (SSS) method, as an alternative to greedy search, to speed up tree construction. RFIT outperforms the traditional 'separate regression' approach in estimating ITE, where the latter approach suffers from a severe bias problem that is not widely noted in the previous literature. Furthermore, standard errors for the estimated ITE via RFIT can be obtained with the infinitestimal jackknife method [2]. We assess and illustrate the use of RFIT via both simulation and the analysis of data from an acupuncture headache trial.

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Innovative Methods for the identification of Predictive Biomarker Signatures in Oncology

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ABSTRACT

We present a procedure based on a set of newly developed statistical methods, for the identification and evaluation of complex multivariate predictors of treatment effect. The procedure is implemented on data collected from two clinical studies AVADO and AVEREL. Both are prospective, randomized clinical trials designed to evaluate the efficacy of bevacizumab on patients with HER2-negative (AVADO) and HER2-positive (AVEREL) metastatic breast cancer. The objective of the analysis is to identify a subgroup of patients who may receive the largest benefit from bevacizumab using a panel of 10 biomarkers measured at baseline. To this end, we first develop a classification rule, based on an estimated individual scoring system, using data from the AVADO study only. In this stage several methods for estimate the individualized treatment effect are discussed and the optimal classification rule is selected via the cross-validation. We then separate the patients in the AVEREL study into the patient group with promising treatment benefit and the patient group without, based on this rule. In the group with promising treatment benefit, the estimated hazard ratio of bevacizumab versus placebo for progression free survival is 0.687 (95% CI, 0.462-1.024, p=0.065), while in the not-promising group the hazard ratio is 1.152 (95% CI, 0.526-2.524, p=0.723). Many reports have discussed the potential of VEGF-A as a predictor of treatment response for bevacizumab. If we simply use the median of VEGF-A to divide the patients of the AVEREL study, then the HR becomes 0.711 (95% CI 0.435-1.163, p=0.174) in the promising group and 0.828 (95% CI 0.496 1.380, p=0.468) in the not-promising group. In conclusion, our constructed scoring system successfully identifies a subgroup of patients who may benefit from bevacizumab and the positive treatment effect within the subgroup can be verified on an independent study. The constructed scoring system performs better than VEGF-A alone in the test data. The proposed procedure has the potential of broad applications in other settings aiming for the development of personalized medicine.

Optimal Combination of Multiple Markers and Applications to Survival Data with Disease-Free Sampling

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ABSTRACT

Disease-free sampling is commonly adopted to recruit study subjects for evaluating marker performance in relation to progression of a disease in observational studies. We consider the problem of how to optimally combine markers to predict time to disease when disease-free sampling is used to recruit study subjects. To characterize the relationship between markers and disease outcome, two different time indices are considered: (i) time from study entry to disease incidence, and (ii) age at time of disease incidence, which respectively result in right-censored data, and left-truncated and right-censored data. It is important to keep in mind that the populations for these two kinds of data, defined at time origin 0 for the respective time index, are different. To emphasize long-term prediction effect, we consider markers which are measured at baseline or a fixed time. For time index (i), in use of the proportional hazards model (Cox, 1972) which involves both markers and covariates, we study composite markers which are combined and derived with various criteria, where the optimality is evaluated by time-dependent receiver operating characteristic (ROC) curve and area under curve (AUC). The optimality of composite markers is also obtained via a global index for assessing the overall performance to predict the disease outcome. When time index (ii) is of interest, questions arise as to how to conceptualize the baseline or fixed-time markers for remote prediction of disease in the future. These questions are discussed in this talk with analytical details. A data example from the markers of Cognitive Decline Among Normal Individuals (BIOCARD) cohort study is used to illustrate the proposed approaches to study markers' predictability for the occurrence of Alzheimer's Disease.

Treatment Recommendation and Parameter Estimation under Single-Index Contrast Function

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ABSTRACT

We consider a semiparametric model for contrast function which is defined as the conditional expected outcome difference under comparative treatments. The contrast function can be used to recommend treatment for better average outcomes. Existing approaches model the contrast function either parametrically or nonparametrically. We believe our approach improves interpretability over the nonparametric approach while enhances robustness over the parametric approach. Without explicit estimation of the nonparametric part of our model, we show that a kernel based method can identify the parametric part up to a multiplying constant. Such identification suffices for treatment recommendation. Our method is also extended to high dimensional settings. We study the asymptotics of the resulting estimation procedure in both low and high dimensional cases. We also evaluate our method in simulation studies and real data analyses.

Generalizing Treatment Strategies from Randomized Trials to Target Populations

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ABSTRACT

Individualized treatment rules based on individual patient characteristics are becoming important in clinical practice. Properly planned and conducted randomized clinical trials are ideal for constructing individualized treatment rules. However, it is often a concern that trial subjects lack representativeness, which limits the applicability of the derived rules to a future large population. Furthermore, to inform clinical practice, it is desirable to provide rules that are easy to interpret and disseminate. To tackle these issues, we use data from a single trial study to propose a two-stage procedure to derive a robust and parsimonious rule to maximize the benefit of future patients. The procedure allows a wide range of possible covariate distributions in the target population, with minimal assumptions on the mean and covariance of the patients who benefit from each treatment. The practical utility and favor- able performance of the methodology are demonstrated using extensive simulations and a real data application.

Interaction-based predictive learning for the genetic etiology of complex diseases

Tian Zheng

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ABSTRACT

Epistasis or gene-gene interaction are known to be a ubiquitous feature of complex diseases. Detection of gene?gene interaction is difficult and computational challenging. In this talk, I will first introduce a framework of prediction-oriented evaluation of gene sets [1] and then discuss how this framework can be applied to search important gene-gene interactions that are predictive of disease risks.

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Bayesian additive decision trees of biomarker-by treatment interactions for predictive biomarkers detection and subgroup identification

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ABSTRACT

Personalized medicine, or tailored therapy, has been an active and important topic in recent medical research. Many methods have been proposed in the literature for predictive biomarkers detection and subgroup identification. In this paper, we propose a novel decision tree based approach applicable in randomized clinical trials. We model the prognostic effects of the biomarkers using additive regression trees and the biomarker-by-treatment effect using a single regression tree. Bayesian approach is utilized to periodically revise the split variables and the split rules of the decision trees, which provides a better overall fitting. Gibbs sampler is implemented in the MCMC procedure, which updates the prognostic trees and the interaction tree separately. We use the posterior distribution of the interaction tree to construct the predictive scores of the biomarkers and to identify the subgroup where the treatment is superior to the control. Numerical simulations show that our proposed method performs well under various settings comparing to existing methods. We also demonstrate an application of our method in a real clinical trial.