International Biostatistics Workshop

July 9, 2018

Program

International Biostatistics Workshop

July 9, 2018, A302 Science Building, ECNU

8:30am – 8:35am
Opening Remark

8:35--9:25 Effect Heterogeneity and Subgroup Identification for Long-Term Interventions, Dr Menggang Yu, Wisconsin-Madison & ECNU

9:25--10:15 Robust Analyses of Over-dispersed Counts with Varying Follow-up in Small Samples and Rare Diseases, Dr Frank Konietschke, University of Texas at Dallas

10:15am – 10:35am
Coffee Break

10:35--11:05 Multi-category Individualized Treatment Regime Using Outcome Weighted Learning, Mr Xinyang Huang, ECNU

11:05--11:35 Selecting Variables with Treatment Interaction, Mr Shiferaw Befkadu, ECNU

12:00pm – 1:00pm
Lunch

1:30--2:10 Quantifying (Niche or Distribution) Overlap: New Concepts and Applications, Dr Arne Bathke, University of Salzburg

2:10--2:50 Multivariate Tests in High Dimensions and Unstructured Dependence, Dr Solomon Harrar, University of Kentucky

2:50pm – 3:20pm
Tea Break

3:20--4:00 A Robust Approach to Sample Size Calculation in Cancer Immunotherapy Trials with Delayed Treatment Effect, Dr Menggang Yu, Wisconsin-Madison & ECNU

4:00--4:30 Basket Trial Designs in Oncology, Dr Huadong Zhao, Pfizer

4:30--5:00 Basket Trial, Umbrella Trial and Platform Trial---An Overview and Case Study, Dr Leslie Meng, Boehringer Ingelheim

5:00pm – 5:05pm
Closing Remark

Abstracts (by presenting order)

Effect Heterogeneity and Subgroup Identification for Long-Term Interventions

Menggang Yu, U. Wisconsin-Madison & ECNU
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There has been great interest in developing interventions to effectively coordinate the typically fragmented care of patients with many comorbidities. Evaluation of such interventions is often challenging given their long-term nature and their differential effectiveness among diverse patient populations. Given this and the resource intensiveness of care coordination interventions, there is significant interest in identifying which patients may benefit the most from care coordination. We accomplish such goal by modeling covariates which modify the intervention effect. In particular, we consider long-term interventions whose effects are expected to change smoothly over time. We allow interaction effects to vary over time and encourage these effects to be more similar over time by utilizing a fused lasso penalty. Our approach allows for flexibility in modeling temporal effects while also borrowing strength in estimating these effects over time. We use our approach to identify a subgroup of patients who benefit from a complex case management intervention in a large hospital system. If time permits, other interesting aspects of personalized health care interventions will also be discussed.

Robust analyses of over-dispersed counts with varying follow-up in small samples and rare diseases

Frank Konietschke, University of Texas at Dallas
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In this talk, we consider inference methods for count data, such as the number of relapses and magnetic resonance imaging (MRI) lesion counts in multiple sclerosis (MS), or exacerbations in chronic obstructive pulmonary disease (COPD). In such clinical trials, the number of exacerbations and the follow-up time is recorded for each patient. Due to the heterogeneity of patients, the number of exacerbations cannot be assumed to follow a Poisson distribution, and over-dispersion has to be taken into account for valid statistical inferences. We derive statistical inference methods for testing null hypotheses as well as for constructing confidence intervals for the underlying treatment effects. For small sample sizes, a studentized permutation approach will be investigated. Extensive simulation studies show that the permutation based statistics tend to maintain the nominal type-1 error level or coverage probability very satisfactorily. A real data set illustrates the application of the proposed methods. The project is in cooperation with Professor Tim Friede, University of Göttingen, and Professor Markus Pauly, University of Ulm.

Multi-category individualized treatment regime using outcome weighted learning

Xinyang Huang, ECNU
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Individualized treatment regimes (ITRs) aim to recommend treatments based on patient-specific characteristics in order to maximize the expected clinical outcome. Outcome weighted learning approaches have been proposed for this optimization problem with primary focus on the binary treatment case. Many require assumptions of the outcome value or the randomization mechanism. In this paper, we propose a general framework for multi-category ITRs using generic surrogate risk. The proposed method accommodates the situations when the outcome takes negative value and/or when the propensity score is unknown. Theoretical results about Fisher consistency and excess risk are established. In practice, we recommend using differentiable convex loss for computational optimization. We demonstrate the superiority of the proposed method under multinomial deviance risk to some existing methods by simulation and application on data from a clinical trial.

Selecting variables with treatment interaction

Shiferaw Befkadu, ECNU
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Consider a regression model with a discrete treatment variable and a number of covariates. It is of interest to select the covariates which have interactions with treatment. We propose a marginal feature ranking and screening procedure for measuring interactions between the treatment and covariates. The method does not require imposing a specific model structure on the regression model and is applicable in a high dimensional setting. Theoretical properties of the proposed method are obtained. Its empirical performance is evaluated by simulation and real data analysis.

Quantifying (Niche or Distribution) Overlap: New Concepts and Applications

Arne Bathke, University of Salzburg
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The problem of quantifying the overlap of niches or distributions has received much attention lately, in

particular in quantitative ecology, from where it also originates. However, the niche concept has the potential to also be useful in many other application areas, as for example in economics. We are presenting a fully nonparametric, robust solution to this problem, along with exact shortcut formulas based on rank-statistics, and with a rather intuitive probabilistic interpretation. Furthermore, by deriving the asymptotic sampling distribution of the estimators, we are proposing the first asymptotically valid inference method, providing confidence intervals for the niche overlap. The theoretical considerations are supplemented by simulation studies and a real data example, and by discussing open questions.

Multivariate tests in high dimensions and unstructured dependence

Solomon Harrar, University of Kentucky
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Recent results for comparison of high-dimensional mean vectors make assumptions that require the dependence between the variables to be weak. This requirement fails to be satisfied, for example, by elliptically contoured distributions. We relax the dependence conditions that seem to be the standard assumption in high-dimensional asymptotic tests. With the relaxed condition, the scope of applicability of the the results broadens. In particular, strong mixing type of dependence and applications for rank-based comparison of groups are covered. For the rank-based methods, hypotheses are formulated in terms of meaningful and easy to interpret nonparametric measures of effect. This formulation accommodates data in binary, discrete, ordinal and continuous scales seamlessly. The problem is setup in a general and flexible form that extension of the results to general factorial design, including repeated measures, are formally illustrated. Simulation studies are used to evaluate the numerical performance of the results in practical scenarios. Data from Electroencephalograph (EEG) experiment is analyzed to illustrate the application of the results.

A Robust Approach to Sample Size Calculation in Cancer Immunotherapy Trials with Delayed Treatment Effect

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Immunotherapies are taking the center stage for cancer drug development and research. Many of these therapies, for example, immune checkpoint inhibitors, are known to have possible lag periods to achieve their full effects. Therefore the proportional hazard assumption is violated when comparing survival curves in randomized clinical trials evaluating such therapies. Limited work exists in determining sample size to account for the lag period which is usually unknown. Assuming that the lag period is within some reasonable range, this talk presents an approach to calculate sample size based on a maximin efficiency robust test. Both theoretical derivations and simulation results show the proposed approach can guarantee the desired power in worst case scenarios and often much more efficient than existing approaches. Application to a real trial design will also be illustrated.

Basket Trial Designs in Oncology

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The basket trial is designed with scientific and statistical rigor to enable the approval of an experimental treatment in multiple tumor indications based on the outcome from a single study. Given the difficulty in indication selection, the basic idea is to prune the inactive indications at an interim analysis and pool the active indications in the final analysis. A critical statistical issue of the basket design is Type I error control for the pooled analysis after pruning. While pruning may be seen as cherry-picking which tends to inflate the Type I error, it also shares similarity with a binding futility analysis which tends to deflate the Type I error if all indications are pruned. The net impact of pruning is complicated. The use of different endpoints for pruning and pooling further complicates the issue. We will share statistical details on Type I error control for the general basket design concept under three sample size adjustment strategies after pruning. Power and sample size calculations are also provided.

Basket Trial, Umbrella Trial and Platform Trial---An Overview and Case Study

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The traditional clinical trial design with one-agent-at-a-time fashion has been challenged due to the substantial progress in the areas of genomics technology, tumor biology, computational analysis, and drug discovery. Statistician Dr. Don Berry stated that “it is ironic that we take the same clinical trial approach to evaluate all manner of potentially amazing transformative experimental therapies and yet we don’t experiment with the design of the clinical trial itself”. Basket trial, umbrella trial and platform trial designs emerged to investigate multiple target-treatment pairs in parallel, either within or across recognized tumor types. This talk will provide an overview of basket trial, umbrella trial and platform trial designs, and a case study.