PROGRAM

Invited Speakers in bold print (40 minutes, otherwise 20 minutes)

Tuesday

Mixer (9 PM-10 PM), Room (TBA)

Wednesday

Session WAM1: Opening Session (8 AM-10 AM), Room: Grand Ball Room A, Chair: Jie Chen	
Jason Hsu *The Ohio State University*	Welcome remarks
Zukang Zheng *Fudan University*	Welcome remarks
Qingwu Jiang *Fudan School of Public Health*	Welcome remarks
Robert O'Neill *CDER, FDA, USA*	Statistical principles and practices in the development of evidence for medical products: challenges for the international community in the 21st century
Chen Yao *Beijing University Hospital*	The biostatistical guidelines for clinical trials in China
Coffee Break (10:00 AM-10:30 AM)	
Session WAM2-I: MCPs in Microarray Data Analysis (10:30 AM-12:00 PM), Room: Grand Ball Room A, Chair: Gene Pennello	
Katherine S. Pollard	Genomic applications of new multiple testing procedures based on a test statistics null distribution
Jason C. Hsu	Multiple comparisons of gene expression levels from designed microarrays and microarray experiments
Dingfeng Jiang	A clinical prognostic prediction of lymph node-negative breast cancer by gene expression profiles
Session WAM2-II: Multiplicity Issues in Clinical Trials (10:30 AM-12:00 PM), Room: Grand Ball Room C, Chair: Zhenming Shun	
Yong-Cheng Wang	Multiplicity issues in oncology mortality trial with treatment crossover
Ning Li	A design methodology for evaluating oncology genomic studies with multiple comparisons issues
Hui Quan	Multiplicity adjustment for clinical trials with two doses of an active treatment and multiple primary and secondary endpoints
Zhenming Shun	Statistical consideration of the strategy for demonstrating clinical evidence of effectiveness ~W one larger vs two smaller pivotal studies
Lunch Break (12:00 PM-1:30 PM)	
Session WPM1-I: Advances in False Discovery Rate (I) (1:30 PM-3:00 PM), Room: Grand Ball Room C, Chair: Yoav Benjamini	
Helmut Finner	Dependency and false discovery rate: Asymptotics

Paul Somerville	FDR procedures controlling the number and proportion of false positives
Daniel Yekutieli	Hierarchical false discovery rate controlling procedures
Tianhui Zhou	Bayes false discovery and false non-discovery rates

Session WPM1-II: Analysis of Safety Data (1:30 PM-3:00 PM), Room: Peony Room, Chair: Willi Maurer

A. Lawrence Gould	Accounting for multiplicity in the evaluation of data mining "signals" from spontaneous adverse event report databases
Xiaoyin Fan	False discovery rate methods for safety analyses in dose-response clinical trials
James Troendle	Testing multiple Bernoulli outcomes with covariates

Coffee Break (3:00 PM-3:30 PM)

Session WPM2-I: MCPs in Regression Problems (3:30 PM-5:00 PM), Room: Grand Ball Room C, Chair: Juliet P. Shaffer

Wei Liu	Regression analysis via confidence bands
Mortaza Jamshidian	A study of the partial F-test for multiple linear regression models
Ying Zhang	A simple multiple comparison procedure for linear regression lines

Session WPM2-II: Clinical Trial Applications (3:30 PM-5:00 PM), Room: Peony Room, Chair: A. Lawrence Gould

Steven Sun	Adjusted p-values for multiple testing of significance in clinical trials
Gene Pennello	Approximate sequential Bayes rules for clinical trials submitted to the US FDA
Guoyong Jiang	On stepwise test procedures for evaluating dose proportionality
Kun Jin	Multiplicity issues in CNS trials

Banquet (6:30 p.m.), Lu Bo Lang Restaurant, Speaker: Charles Dunnett

Thursday

Session TAM1-I: Applications of Partitioning Principle (8:30 AM-10:00 AM), Room: Grand Ball Room C, Chair: Helmut Finner

Klaus Strassburger	Improved fixed ordered testing procedures based on the partitioning principle
Xiang Ling	Adaptive design of dose-response studies using the partitioning principle
Haiyan Xu	Using the partitioning principle to control generalized familywise error rate

Session TAM1-II: Applications of FDR to Microarray Data Analysis (8:30 AM-10:00 AM), Room: Peony Room, Chair: Katie Pollard

Vishwanath Iyer	An adaptive single-step FDR procedure with applications to DNA microarray analysis
Øyvind Langsrud	Adjusted p-values by rotation testing
Anat Reiner	Complexity of data and analysis related to FDR control in microarray experiments
Colin (Lin) Chen	Growth charts of body mass index (BMI) with quantile regression

Coffee Break (10:00 AM-10:30 AM)

Session TAM2-I: Stepwise Test Procedures (10:30 AM-12:00 PM), Room: Grand Ball Room C, Chair: Wei Liu

Koon-Shing Kwong	Stepwise multiple test procedures for the directional-mixed families

Tsunehisa Imada	Multiple comparisons for normal mean vectors based on a step-down procedure
Weizhen Wang	Step-down tests procedures in orthogonal saturated designs
Samuel Wu	Step-up simultaneous tests

Session TAM2-II: Large Scale Multiplicity Problems (I) (10:30 AM-12:00 PM), Room: Peony Room, Chair: Wenjin Wang

Martin Posch	Two-stage designs for experiments with a large number of hypotheses
Ji-Qian Fang	Sequential decision tree based on trichotomy - an alternative approach of multiple comparisons
Peter Westfall	Optimal data snooping: Is Bonferroni admissible for large k?

Lunch Break (12:00 PM-1:30 PM)

Session TPM1-I: Multiple Endpoints (1:30 PM-3:00 PM), Room: Peony Room, Chair: Ajit Tamhane

Lang Wu	Some improved tests for multivariate one-sided hypotheses
Xun Chen	The application of enhanced parallel gatekeeping strategies
Susan Li	A modified gatekeeping strategy and its application in testing multiple families of hypotheses in a clinical trial

Session TPM1-II: Theoretical Aspects of MCPs (1:30 PM-3:00 PM), Room: Grand Ball Room C, Chair: Jason C. Hsu

Juliet Shaffer	Multiple requirements for multiple test procedures
Debashis Ghosh	Multiple testing and shrinkage estimation
Jeen Liu	Power calculation for MCPs of three Binomials
Vered Madar	Simultaneous confidence intervals for multiple parameters with more power to determine the sign

Coffee Break (3:00 PM-3:30 PM)

Session TPM2-I: Advances in False Discovery Rate (II) (3:30 PM-4:40 PM), Room: Grand Ball Room C, Chair: Daniel Yekutieli

Yoav Benjamini	An FDR point of view on multiplicity problems in clinical trials
Sanat Sarkar	Two-stage FDR procedures

Session TPM2-II: Adaptive Designs (3:30 PM-4:40 PM), Room: Peony Room, Chair: Steve Sun

Willi Maurer	Confirmatory seamless phase II/III clinical trials with treatment selection at interim
Gang Chen	Adaptive design for sample size re-estimation using a fixed calendar time
Gerhard Hommel	Control of the false discovery rate in adaptive designs

The Shanghai Acrobat Show (TIME)

Friday

Session FAM1-I: Bayesian MCPs (8:30 AM-10:00 AM), Room: Grand Ball Room C, Chair: Peter Westfall

Gene Pennello	Bayes rule multiple comparison procedures: A simpler life
Jie Chen	On Bayesian multiple testing of two-way layouts
Shu Han	Budget impact analysis using a Bayesian approach
Jianhua Hu	Bayesian model selection using F-statistics

Session FAM1-II: Isotonic Inference Problems (8:30 AM-10:00 AM), Room: Peony Room, Chair: Frank Bretz	
Chihiro Hirotsu	Inference on the isotonic contrasts based on max acc. t statistic
Yanqin Feng	Multi-sample testing for the equality of multinomial populations against increasing convex ordering alternative
Tetsuhisa Miwa	The evaluation of normal orthant probabilities with singular correlation matrices
Yoshiro Yamamoto	An optimum linear test statistic of the homogeneity against the simple loop order on a (p, q) array
Coffee Break (10:00 AM-10:30 AM)	
Session FAM2-I: Change Point and Selection Problems (10:30 AM-12:00 PM), Room: Grand Ball Room C, Chair: Jie Chen	
Fahimah Al-Awadhi	On the performance of logrank tests for change point
Haiyan Cai	Issues in confidence intervals for largest means
Tomohiro Nakamura	Group sequential procedure to find the changing population mean
Jianan Peng	A new approach to subset selection for normal treatments
Session FAM2-II: Dose Response Problems (10:30 AM-12:00 PM), Room: Peony Room, Chair: Xiaoyin Fan	
Frank Bretz	Combining multiple comparisons and modeling techniques in dose response studies
Jiandong Lu	Hierarchical testing procedures for the analysis of individual doses for clinical trials with multiple endpoints
Bei Zhou	Multiplicity adjustments for clinical trials with 2 doses for an active treatment and a placebo control
Brian Yan	Multiple tests for comparison of several doses with a zero-dose control
Lunch Break (12:00 PM-1:30 PM)	
Session FPM1-I: Large Scale Multiplicity Problems (II) (1:30 PM-2:40 PM), Room: Grand Ball Room C, Chair: Haiyan Xu	
Toshinari Kamakura	Simulation studies of random fields designed for brain image analysis
Kyung In Kim	Estimating the FDR for interval null-hypotheses using nonparametric deconvolution
Keith Worsley	Giant multiple comparison problems with random field data in brain mapping and 'bubbles"
Session FPM1-II: Applications of MCPs to Genomic Problems (1:30 PM-2:40 PM), Room: Peony Room, Chair: Guohua Pan	
Jiashun Jin	Sparse inference in large scale multiple comparisons and FDR thresholding
Wu Jing	Coding Exon detection using comparative sequences
Christoph Lange	Genomic screening in family based association testing

A B S T R A C T S

(Alphabetic by author)

Speaker: Fahimah Al-Awadhi

Session FAM2-I: Change Point and Selection Problems (Friday, 10:30 AM-12:00 PM), Chair: Jie Chen

Co-Author: F. Al-Awadhi and E. ALY

Institute: Kuwait University

Category: Nonparametrics

Title: On the performance of logrank tests for change point

Abstract: We consider the problem of a change point when the data is randomly censored from the right based on an extension of the logrank test. We compare the performance of this technique with other known techniques using a Large scale Monte Carlo Study for different combination of distributions. We apply the logrank change point technique on a real data problem; the Stanford heart transplantation data.

Speaker: Yoav Benjamini

Session TPM2-I: Advances in False Discovery Rate (II) (Thursday, 3:30 PM-4:40 PM), Chair: Daniel Yekutieli

Co-Author:

Institute: Tel Aviv University

Category: Error rates If others: Also Multiple Endpoints

Title: An FDR point of view on multiplicity problems in clinical trials

Abstract: I shall discuss the concerns about simultaneous and selective inference in the analysis of primary, secondary and tertiary endpoints in clinical trial. I shall emphasize where FDR control is appropriate and where it is not. The use of weighted FDR for that purpose will be illustrated, relying on some new results regarding the procedure that controls it.

Speaker: Frank Bretz

Session FAM2-II: Dose Response Problems (Friday, 10:30 AM-12:00 PM), Chair: Xiaoyin Fan

Co-Author: José Pinheiro

Institute: Novartis Pharma AG

Category: Clinical trials

Title: Combining multiple comparisons and modeling techniques in dose response studies

Abstract: The analysis of dose response studies has long been divided according to two major strategies: multiple comparison procedures and model-based approaches. The model-based approach assumes a functional relationship between the response and the dose, taken as a quantitative factor, according to a pre-specified parametric model. The fitted model is then used to estimate an adequate dose to achieve a desired response. Such an approach provides flexibility in investigating the effect of doses not used in the actual study. However, the validity of its conclusions will highly depend on the correct choice of the a-priori unknown dose-response model. This creates a dilemma within the regulated environment in which drug development takes place, since it is required to have the analysis methods (including the choice of the dose-response model) defined prior to the study. Multiple comparison procedures, on the other hand,

regard the dose as a qualitative factor and make very few, if any, assumptions about the underlying dose-response model. The primary goal is often to identify the minimum effective dose that is statistically significant and produces a clinically relevant effect. One approach is to evaluate the significance of contrasts between different dose levels, while preserving the familywise error rate. Such procedures are relatively robust to the underlying dose-response shape, but they are not designed for extrapolation of information beyond the observed dose levels. Inference is thus confined to the selection of the target dose among the dose levels under investigation. In this talk, we describe a unified strategy to the analysis of data from dose-response studies which combines multiple comparison and modeling techniques. We assume the existence of several candidate parametric models and use multiple comparison techniques to choose the one most likely to represent the true underlying dose-response curve. Such a procedure allows the selection of the most adequate dose-response model within the candidate set, while preserving the familywise error rate. The selected model is then used to provide inference on adequate doses, as described above. The methods will be illustrated with data from a phase II dose-finding study. Extensive simulations describe the operating characteristics of the new procedure.

Speaker: Haiyan Cai

Session FAM2-I: Change Point and Selection Problems (Friday, 10:30 AM-12:00 PM), Chair: Jie Chen

Co-Author:

Institute: University of Missouri - St. Louis

Category: Applications

Title: Issues in confidence intervals for largest means

Abstract: Suppose there are N normal populations with N being large. We are interested in estimating the K largest means of these populations, where K is a number typically much smaller than N. In this talk we will discuss issues in searching for procedures that allow us to construct confidence intervals for these quantities simultaneously with good coverage probabilities.

Speaker: Colin (Lin) Chen

Session TAM1-II: Applications of FDR to Microarray Data Analysis (8:30 AM-10:00 AM), Chair: Katie Pollard

Co-Author:

Institute: SAS Institute Inc.

Category: Applications

Title: Growth charts of body mass index (BMI) with quantile regression

Abstract: Growth charts of body mass index (BMI) are constructed from the recent four-year national cross-sectional survey data (1999$-$2002) using parametric quantile regression methods, which are implemented with a newly developed SAS procedure (http://www.sas.com/statistics) and SAS macros.

Speaker: Gang Chen

Session TPM2-II: Adaptive Designs (Thursday, 3:30 PM-4:40 PM), Chair: Steve Sun

Co-Author: Kevin Liu and George Chi

Institute: Johnson & Johnson PRD, Clinical Biostatistics

Category: Clinical trials

Title: Adaptive design for sample size re-estimation using a fixed calendar time

Abstract: The timing for the sample size re-estimation in a two stage adaptive design depends on a pre-specified proportion of information collected in the first stage of a trial. However, in practice the decision for the increase of sample size needs to be made before the enrollment of patients has been ended. For example, if accrual time planned for a trial is 18 month, then the latest time for the decision of sample size adjustment should be made at (or around) the 15th month of the accrual. At least 3 month is needed for data cleaning, statistical analyses, and management decision. Adaptive design based on a given calendar time guarantees that the enrollment will not be stopped before the decision made for the increase of sample size. The major issue using a fixed calendar time for interim analysis is that the information collected at a fixed calendar time can not be pre-specified in the trial design and it becomes a random variable. The adaptive design methods available so far, however, are all based on a fixed proportion of information (e.g., 50% of information). In this presentation, a two stage design for sample size re-estimation based on a fixed calendar time (random information) is proposed and the appropriate type I error adjustment has also been discussed.

Speaker: Jie Chen

Session FAM1-I: Bayesian MCPs (Friday, 8:30 AM-10:00 AM), Chair: Peter Westfall

Co-Author: Xin Gao, York University

Institute: Merck Research Laboratories

Category: Bayesian methods

Title: On Bayesian multiple testing of two-way layouts

Abstract: With two-way layout data, one often is interested in (1) whether there is an overall significant treatment effect at each level of another variable, and (2) if the answer to (1) is ``yes'' at some levels, then how to rank the treatment effects within each ``significant'' level. To answer both questions simultaneously could be a difficult task for a frequestist because of the complexity of multiplicity issue. In this research we extend Berger and Deely (1988)'s Bayesian approach to ranking and selection in one-way ANOVA to two-way layouts and focus on (1) the development of Bayes factors for rejecting a null hypothesis, (2) the properties of the posterior probabilities of the null and alternative hypotheses, and (3) the Bayesian ranking of treatment effects. The approach is illustrated using two real data sets, one from clinical trial involving multiple treatments and many adverse events and the other from a microarray experiment comparing gene expressions among tumor types for thousands of genes.

Speaker: Xun Chen

Session TPM1-I:Multiple Endpoints (Thursday, 1:30 PM-3:00 PM), Chair: Ajit Tamhane

Co-Author: Xiaohui Luo and Tom Capizzi

Institute: Merck & Co., Inc.

Category: Closed testing and partitioning principle

Title: The application of enhanced parallel gatekeeping strategies

Abstract: The parallel gatekeeping strategy proposed by Dmitrienko et al.provides a flexible framework for the pursuit of strong control on study wise type I error rate. This paper further explores the application of the weighted Simes parallel gatekeeping procedure recommended by Dmitrienko et al. and proposes some modifications to it to better incorporate the interrelationships of different hypotheses in actual clinical trials and to achieve better power performance. We first propose a simple method to quantitatively control the impact of secondary tests on the testing of primary hypotheses. We then introduce a matched gatekeeping procedure to exemplify how to address special relationships between individual primary and secondary tests following the parallel gatekeeping framework. Our simulation study demonstrates that the enhanced gatekeeping procedures generally result in more powerful tests than the parallel gatekeeping procedure in Dmitrienko et al. whenever applicable.

Speaker: Xiaoyin Fan

Session WPM1-II: Analysis of Safety Data (Wednesday, 1:30 PM-3:00 PM), Chair: Willi Maurer

Co-Author: Devan V. Mehrotra and Robin Mogg

Institute: Merck & Co., Inc.

Category: Error rates

Title: False Discovery Rate methods for safety analyses in dose-response clinical trials

Abstract: When there are multiple comparisons being performed simultaneously, control of the false discovery rate (FDR), as proposed by Benjamini and Hochberg (1995), is a useful alternative to controlling the family-wise type I error rate. In a typical analysis of safety data in a controlled clinical trial, the multiple comparison issue is especially important because the number of adverse experiences (AEs) is usually so large that even the FDR adjustment may be too conservative. In this case, a novel Double FDR method proposed by Mehrotra and Heyse (2004) can be adopted if predetermined categories are available to group the AEs, e.g. by body system. In this presentation, we will discuss application of the Double FDR methodology to clinical trials where increasing doses of a drug or vaccine are compared with placebo. Analyses of safety data from Merck^Òs phase I HIV vaccine trials will be used for illustration.

Speaker: Ji-Qian Fang

Session TAM2-II:Large Scale Multiplicity Problems (I) (Thursday, 10:30 AM-12:00 PM), Chair: Wenjin Wang

Co-Author: Mei Jiang

Institute: Sun Yat-Sen University

Category: Decision theory

Title: Sequential decision tree based on trichotomy - an alternative approach of multiple comparison

Abstract: Classical discriminant analysis belongs to the classifier which judges only once based on a decision rule that divides the space into two parts. And the application of discriminant function always requires the information of all variables for every individual. Decision tree uses variables one by one to make decisions sequentially. But the decision rules of the currently existing decision tree algorithms only use one variable in each inner node, and assume the variables are independent one another so that the information of correlation among variables can not be utilized sufficiently. Base on the thought of trichotomy (Kendall (1975) and Ji-Qian Fang (1979)), this article proposed a sequential decision tree algorithm which combines the advantages of classical Fisher's discriminant analysis and decision tree: According to the information of an optimal variable or an optimal combination of variables to divide the space into three regions at each step, two decision regions and one awaiting region; if the individual is falling in anyone of two decision regions then make affirmative classification, otherwise make it lie over waiting for a new variable is selected; the optimal combination of the former used variables and the new one is used within the awaiting region for the lie over individuals as the next step; the process is continuously repeated until certain criteria are met. Simulation experiments and real examples indicate that this trichotomy-based decision tree algorithm is superior to classical Fisher's discriminant analysis and commonly used algorithm of classification and regression tree (CART) in terms of less misclassification and less number of variables used. And this can be an alternative approach towards the needs of multiple comparison.

Speaker: Yanqin Feng

Session FAM1-II:Isotonic Inference Problems (Friday, 8:30 AM-10:00 AM), Chair: Frank Bretz

Co-Author: Jinde Wang

Institute: Nan Jing University

Category: Stochastic Ordering

Title: Multi-sample testing for the equality of multinomial populations against increasing convex ordering alternative

Abstract: Trend testing has been a central problem in medicine. Stochastic orderings have been widely studied in medicine and the following three orderings are commonly used. The first is monotonicity of the mean function of the response as the exposure is increasing. This kind of study has been done in huge number of papers. However, the comparison based on means only is not informative enough. The second is interested in the probability of getting into better (or worse) situation. There are also lots of papers devoting to the study of monotonicity of this kind of probability. However, the approaches for binary responses tables suffer from the lack of a clear choice for the collapsing. The third is simple stochastic ordering for multinomial populations, most work deals with comparing two populations and only a few peoples considered the distribution theory of test statistic for multi-sample cases. In contrast to the stochastic orderings listed above, the inference for the increasing convex ordering is not known very well though many applications have been found in medicine, and a great deal of applications of the increasing convex ordering are presented in insurance, queuing theory, reliability, operations and so on. Statistical inference methods based on likelihood ratio principle on increasing convex ordering for more than two multinomial populations have not been fully developed. The problem of testing the increasing convex ordering against no restriction for multi-sample case has been considered by using likelihood ratio test. It may be of more interest to test for the equality against the increasing convex ordering alternative among several populations. Moreover, testing for the equality against some stochastic ordering is most commonly considered by statisticians. This paper considers the equality against the increasing convex ordering for multi-sample case. Suppose that $X_1,...,X_m$ are independent multinomial populations, having a common value set $\{b_1,..., b_{k+1}\}$ with $b_1 <\cdots< b_{k+1}$. Let $p_{ij} = P\{X_i = b_j\}$; $p_i =(p_{i1},\cdots,p_{i,k+1})'$ for $i=1,\cdots,m.$ We want to test \begin{equation} p_1=\cdots=p_m\quad against\quad p_1\leq_{cx}\cdots\leq_{cx} p_m \end{equation} we first transform problem (1) into a polyhedral cone-constrained problem, then depending on an optimization method, by using some limit laws and the continuous mapping theory, we obtain the desired null asymptotic distribution of the likelihood ratio test statistic for problem (1), which is the chi-square-bar distribution.

Speaker: Helmut Finner

Session WPM1-I:Advances in False Discovery Rate (I) (Wednesday, 1:30 PM-3:00

PM), Chair: Yoav Benjamini

Co-Author: Roters, Markus

Institute: German Diabetes Center, Duesseldorf , Germany

Category: Error rates (False discovery rate)

Title: Dependency and False Discovery Rate: Asymptotics

Abstract: Over the last decade, some effort has been undertaken to show that the linear step-up procedure (LSU) for testing n hypotheses controls the false discovery rate when test statistics are dependent. In this paper we investigate the expected error rate and the false discovery rate of the LSU-procedure when n tends to infinity. We consider the situation where test statistics are exchangeable under true null hypotheses and where a proportion of null hypotheses is totally false. Among others, we investigate equi-correlated normal and t-variables, respectively. Based on the empirical distribution function of the corresponding p-values we derive several results for the asymptotic EER and FDR. The resulting formulas allow a numerical calculation of the asymptotic behavior of EER and FDR, respectively.

Speaker: Debashis Ghosh

Session TPM1-II: Theoretical Aspects of MCPs (Thursday, 1:30 PM-3:00 PM), Chair: Jason C. Hsu

Co-Author: Wei Chen, Trivellore Raghunathan

Institute: University of Michigan, Department of Biostatistics

Category: Bayesian methods

Title: Multiple testing and shrinkage estimation

Abstract: With recent developments in genomics and high-throughput experimentation technology, there has been a lot of interest in the development of new multiple testing comparison procedures, particular with respect to the false discovery rate. In this talk, we discuss the link between quantities from multiple testing with existing procedures. These links motivate new multiple comparison procedures.

Speaker: A. Lawrence Gould

Session WPM1-II: Analysis of Safety Data (Wednesday, 1:30 PM-3:00 PM), Chair: Willi Maurer

Co-Author:

Institute: Merck & Co., Inc.

Category: Bayesian methods

Title: Accounting for multiplicity in the evaluation of data mining "signals" from spontaneous adverse event report databases

Abstract: The clinical trials undertaken during the development of pharmaceutical products generally are not large enough to identify rare potential toxicities associated with the use of a product. For this reason, postmarketing surveillance always is carried out on a continuing basis once a product has been approved. One component of the surveillance activity is the accumulation of reports sent in by physicians and other health professions of adverse events reported by patients, along with the set of medications the patient was on at the time, in large spontaneous report databases. Although these databases are statistically deficient in a number of ways, they do contain millions of reports and it generally is accepted that the mass of accumulated information is large enough to identify possible drug-event relationships that can be investigated intensively by physicians and epidemiologists. Recently developed pure and empirical Bayes methods provide a way to summarize the data in these databases, including a quantitative measure of the strength of the reporting association between the drugs and the events. Determining which of the drug-event pairs, of which there may be many tens of thousands, represent real reporting associations and which random noise presents a substantial problem of multiplicity because the resources available for medical and epidemiologic followup are limited. The issues are similar to those encountered with the evaluation of microarrays, but there are important differences. The purpose of this presentation is to address some of these issues, including a consideration of what constitutes a ~Qnull hypothesis~R, and to evaluate the performance of currently available methods for dealing with multiplicity arising from very many comparisons. We find that, as with microarrays, there are important connections between methods based on the False Discovery Rate principle and Bayesian principles.

Speaker: Shu Han

Session FAM1-I: Bayesian MCPs (Friday, 8:30 AM-10:00 AM), Chair: Peter Westfall

Co-Author: YCT Shih, Associate Professor, UT M.D. Anderson Cancer Cente

Institute: Rice University

Category: Bayesian methods

Title: Budget impact analysis using Bayesian approach

Abstract: An inhomogeneous Markov Chain model was proposed to incorporate variations in patient mixes and drug prices over time into a Budget Impact Analysis (BIA) using Bayesian methods. The model contains three Markov states categorized by whether a patient^Òs illness was treated with a generic drug, an existing brand-name drug, or a new brand-name drug. During each cycle, the model modifies the patient cohort by accounting for newly diagnosed incident cases as well as changes in exiting cases due to cure or death. A possible change in the drug utilization pattern between current patients and newly diagnosed patients is also considered. A case study based on a simulated dataset was used to compare the budget impact of including a new brand-name drug versus excluding a new brand-name drug in a health care plan; the study assumed a payer^Òs perspective and a five-year time frame. Results are presented in a probabilistic plot similar to the Bayesian cost-effectiveness acceptability curve. We found that adding a new brand-name drug to a health care plan was associated with positive budget savings that increased over time. The proposed model provides an analytical framework for Budget Impact Analysis that tracks the variations in drug utilization over time. Key words: inhomogeneous Markov Chain, budget impact analysis, Bayesian, generic entry, economic evaluations.

Speaker: Chihiro Hirotsu

Session FAM1-II:Isotonic Inference Problems (Friday, 8:30 AM-10:00 AM), Chair: Frank Bretz

Co-Author: Yamamoto, Shouichi

Institute: Meisei University

Category: Clinical trials or Dose response analysis

Title: Inference on the isotonic contrasts based on max acc. t statistic

Abstract: The purpose of the dose response analysis in a phase 2 clinical trial is to prove anyway a monotone response with increasing dose, specify the dose reponse pattern and then choose an optimal dose for the actual clinical treatment. Then a multiple comparisons approach should be preferred rather tha those based on models like logistic regression. In this talk we discuss what patterns of dose response should be taken into consideration as the basic components in the maximal contrast type test.Christoph Lange

Speaker: Gerhard Hommel

Session TPM2-II: Adaptive Designs (Thursday, 3:30 PM-4:40 PM), Chair: Steve Sun

Co-Author: Victor, Anja

Institute: University of Mainz, Germany

Category: Bioinformatics/Genomics

Title: Control of the False Discovery Rate in adaptive designs

Abstract: In many genetical studies, as in the analysis of microarrays or genetic epidemiology, lots of statistical tests have to be performed. In these applications it is common practice to control the FDR rather than the FWER, e.g. by means of the "explorative Simes test" (Benjamini / Hochberg, 1995). Often it seems to be useful to perform at least one interim analysis, and to continue using techniques of adaptive designs. In adaptive designs, it is possible to determine final p-values ("global p-values"; see Liu / Chi, 2001, and Brannath / Posch / Bauer, 2002) and to use them in the final analysis. However, the problem arises that it is not known at an interim analysis how "small" a p-value has to become, since the bounds of the FDR-controlling procedure depend on the number of rejectable hypotheses. We develop a general concept of defining global p-values by means of "global rejection regions". We show that, under certain conditions, procedures for adaptive designs can be constructed giving information about a "worst case" global p-value already at an interim analysis

Speaker: Jason Hsu

Session WAM2-I: MCPs in Microarray Data Analysis (Wednesday, 10:30 AM-12:00 PM), Chair: Gene Pennello

Co-Author: Kristin Bergsteinsdottir, Jane Chang,Magnús Karl Magnússon, Eiríkur Steingrímsson, Sigridur Valgeirsdottir, Tao Wang

Institute: The Ohio State University, Department of Statistics

Category: Bioinformatics/Genomics

Title: Multiple comparisons of gene expression levels from designed microarrays and microarray experiments

Abstract: Commercial use of microarray for prognostic and diagnostic purpose is fast becoming a reality. Such uses of microarrays should meet the usual regulatory requirements for medical devices. We view the process of building microarrays for medical prognostic and diagnostic as in vitro clinical trials. To increase sensitivity and specificity, as well as to facilitate modeling-based multiple comparisons, we design microarrays and training microarray experiments according to the statistical principles of randomization, replication, and blocking. Each oligonucleotide microarray we synthesize contains replicates of probe sets for the target genes. The placement of the probes are randomized. The cRNA sample from each subject is split into parts, and placed onto different microarrays according to an optimal design. Results of our proof-of-concept experiments are analyzed in an R package called MultiArray

Speaker: Jianhua Hu

Session FAM1-I: Bayesian MCPs (Friday, 8:30 AM-10:00 AM), Chair: Peter Westfall

Co-Author: Valen E. Johnson

Institute: University of Texas M.D. Anderson Cancer Center

Category: Bayesian methods

Title: Bayesian model selection using F statistics

Abstract: Bayes factors play an essential role in Bayesian model selection. Usually, the definition of Bayes factors depends critically on the specification of proper prior distributions implicit to both null and alternative hypotheses. We propose a novel approach for computing Bayes factors based on modeling test statistics, thereby eliminating the need to specify a prior distribution under the null hypothesis, and simplifying the specification of the prior under the alternative. We show that this approach retains approximate coherency, a desirable property in the model selection problem. We compare our method to several other Bayesian and frequentist model selection methods and find that it performs similarly to more traditional Bayesian approaches, while at the same time selecting models with better predictive properties than the frequentist procedures.

Speaker: Tsunehisa Imada

Session TAM2-I:Stepwise Test Procedures (Thursday, 10:30 AM-12:00 PM), Chair: Wei Liu

Co-Author: Hideyuki Douke

Institute: Kyushu Tokai University

Category: Designs (adaptive, optimal, sequential, etc.)

Title: Multiple comparison for normal mean vectors based on step down procedure

Abstract: We consider multiple comparison for several normal mean vectors. Specifically we construct multiple comparison procedures by using step down procedures. We give some numerical examples.

Speaker: Vishwanath Iyer

Session TAM1-II: Applications of FDR to Microarray Data Analysis (Thursday, 8:30 AM-10:00 AM), Chair: Katie Pollard

Co-Author: Dr. Sanat Sarkar

Institute: Bristol Myers Squibb / Temple University

Category: Error rates

Title: An adaptive Single-step FDR procedure with applications to DNA microarray analysis

Abstract: One of the areas that has been receiving a lot of recent attention is the use of multiple hypothesis testing procedures in DNA microarray analysis. The primary focus has been on FDR controlling procedures, since the microarray experiments are very exploratory by nature, and the researchers are more interested in controlling the rate of false positives rather than control the probability of making a single erroneous decision. In this paper, we employ the asymptotic approximation of the BH procedure first proposed by Genovese and Wasserman to microarray data that is assumed to come from a mixture of two normal distributions with unknown means and mixing proportions. The adaptive procedure proposed in this paper is as follows: we use the EM algorithm to first estimate the means and mixing proportions from the data which we then use to compute the critical value. Once we have the new threshold value, we then reject all the hypotheses with a p-value smaller than this threshold value. We will compare this procedure with the SAM thresholding procedure. We will also present an argument for claiming that this procedure controls the FDR, and will show this to be true using a simulation study.

Speaker: Mortaza Jamshidian

Session WPM2-I: MCPs in Regression Problems (Wednesday, 3:30 PM-5:00 PM), Chair: Juliet P. Shaffer

Co-Author: Wei Liu

Institute: California State University, Fullerton

Category: Theory and foundations

Title: A study of partial F test for multiple linear regression models

Abstract: Partial F tests play a central role in model selections in multiple linear regression models. This paper studies the partial F tests from the view point of simultaneous confidence bands. It first shows that there is a simultaneous confidence band associated naturally with a partial F test. This confidence band provides more information than the partial F test and the partial F test can be regarded as a byproduct of the confidence band. This view point of confidence bands also leads to insights on the weaknesses of the partial F tests and hence the improvements. The power of the new test will be compared to that of the partial F test. Computer programmes have been developed that implement these new confidence band based inferential methods. An illustrative example will be provided.

Speaker: Dingfeng Jiang

Session WAM2-I: MCPs in Microarray Data Analysis (10:30 AM-12:00 PM), Chair: Gene Pennello

Co-Author: Naiqing Zhao

Institute: Fudan University

Category: Bioinformatics/Genomics

Title: A clinical prognostic prediction of lymph node-negative breast cancer by gene expression profiles

Abstract: For the purpose of setting up a microarray method to predict the prognostic status of breast cancer patients on the basis of genes as few as possible, but maintaining the power of prediction. The present study employs a three-step discrimination method based on a resampling technique to select the prognostic gene markers. We have found 13 genes as the most useful ones to predict the clinical outcome of breast cancer patients with lymph node-negative. Another two datasets are used to testify the predictive power of these 13 genes. The cross-validation of the two datasets shows a good agreement between the predictive results and the clinical outcomes. Kaplan-Meier method and log-rank test further illustrate strong correlation of the predictive results to the time of relapse and its overall survival. In order to further discuss the application of the proposed three-step discrimination, we also generate several simulated datasets, considering the different situations in the microarray

Speaker: Guoyong Jiang

Session WPM2-II: Clinical Trial Applications (Wednesday, 3:30 PM-5:00 PM), Chair: A. Lawrence Gould

Co-Author: Jianjun (David) Li & Lilliam Kingsbury

Institute: Cephalon, Inc

Category: Clinical trials

Title: On stepwise test procedures for evaluating dose proportionality

Abstract: Dose proportionality of a therapeutic product implies that the pharmacokinetic measure of total (AUC) or maximal (Cmax) systemic exposure to the product increases proportionally with dose. Failure to conclude dose proportionality over a given range often prompts further investigation to identify a subset of the range over which dose proportionality prevails. For this purpose, we suggest some stepwise test procedures that strongly control the familywise error rate.

Speaker: Jiashun Jin

Session FPM1-II: Applications of MCPs to Genomic Problems (Friday, 1:30 PM-2:40 PM), Chair: Guohua Pan

Co-Author: David Donoho

Institute: Purdue University

Category: Decision theory (Nonparametrics)

Title: Sparse inference in large scale multiple comparisons and FDR thresholding

Abstract: Control of the False Discovery Rate} (FDR) is a recent innovation in multiple hypothesis testing, allowing the user to limit the fraction of rejected null hypotheses which correspond to false rejections (i.e. false discoveries). The FDR principle also can be used in multiparameter estimation problems to set thresholds for separating signal from noise when the signal is sparse. Success has been proven when the noise is Gaussian; see Abramovich, Benjamini, Donoho and Johnstone (2000). In this talk, we consider the application of FDR thresholding to sparse signals in general additive noise, in hopes of learning whether the good asymptotic properties of FDR thresholding as an estimation tool hold more broadly than just at the Gaussian model. We consider n independent observations $X_i = \mu_i + \eps_i$, $i=1,\dots, n$, where $\mu_i \geq 0$ are individual signals; the vector $\mu = \{ \mu_1, \mu_2, \ldots, \mu_n\}$ is thought to be sparse, with most coordinates 0 and a small fraction significantly larger than 0. We assume the noise $\eps_i $ are iid from a density function $g_0(x)$. We develop an estimation theory using the per-coordinate mean-squared error to measure risk. We consider minimax estimation over parameter spaces defined by constraints on the per-coordinate ℓ^p-norm: $\frac{1}{n} \sum_i^n \mu_i^p \leq \eta^p$. Members of such spaces are vectors μ which are sparsely heterogeneous. We find that the key property that drives the optimality of FDR thresholding is the {\it monotone likelihood ratio} (MLR), i.e. if the likelihood ratio $g_0(x-\mu_2)/g_0(x - \mu_1)$ is strictly monotone for any $\mu_2 > \mu_1$, then for large n and small η, the FDR thresholding is nearly minimax, increasingly so as η decreases. Moreover, the FDR control parameter $0 < q < 1$ plays an important role: the FDR thresholding is nearly minimax when $q \leq \frac{1}{2}$, while choosing a fixed $q > \frac{1}{2}$ prevents near minimaxity. We also show that there are examples of non-MLR families where the largest observations do not contain the non-null data; instead the non-null data are intermediate between the bulk and the extreme tails. This phenomenon motivates some new tools for estimation. We compare our results with work in the Gaussian setting by Abramovich, Benjamini, Donoho, Johnstone (2000)

Speaker: Kun Jin

Session WPM2-II: Clinical Trial Applications (Wednesday, 3:30 PM-5:00 PM), Chair: A. Lawrence Gould

Co-Author:

Institute: US Food and Drug Adminstration, CDER

Category: Multiple endpoints problems

Title: Multiplicity issues in CNS trials

Abstract: Recently, more drug companies have been seeking to add additional efficacy claim(s) to their drug labeling. These claims include clinical benefits in different domains than the primary claim, quick drug onsets, longer treatment durations, and particular safety profiles. This talk will illustrate some statistical and regulatory challenges facing CNS trials. Recent practices that have handled the claims on more than one endpoint will be discussed, with emphasis on the separation of clinical concerns from statistical problems. The multiplicity issues involved with early onset claims and related clinical concerns will also be discussed, as well as the preferred global test for the multiple doses trial and its potential shortcomings.

Speaker: Wu Jing

Session FPM1-II: Applications of MCPs to Genomic Problems (Friday, 1:30 PM-2:40 PM), Chair: Guohua Pan

Co-Author: David Haussler

Institute: Purdue University, Department of Statistics

Category: Bioinformatics/Genomics

Title: Coding Exon detection using comparative sequences

Abstract: We introduce a new system, called shortHMM, for predicting exons, which predicts individual exons using two related genomes. In this system, we build a hidden semi-Markov model to identify exons. In the hidden Markov model, we propose joint probability models of nucleotides in introns, splice sites, 50UTR, 30UTR and intergenic regions by exploiting the homology between related genomes. In order to reduce the false positive rate of the hidden Markov model, we develop a screening process which is able to identify intergenic regions. We then build a classifier by combining the statistics from the hidden Markov model and the screening process. We implement shortHMM on human-mouse sequence alignments. Compared to TWINSCAN and SLAM, shortHMM is substantially more powerful in identifying AT-rich RefSeq exons (8% more AT-rich RefSeq exons were predicted), as well as slightly more powerful in identifying RefSeq exons (3%-10% more RefSeq exons were predicted), at a similar or lower false positive rate, with less computing time and with less memory usage. Last, shortHMM is also capable of finding new potential exons.

Speaker: Toshinari Kamakura

Session FPM1-I: Large Scale Multiplicity Problems (II) (Friday, 1:30 PM-2:40 PM), Chair: Haiyan Xu

Co-Author: Tomoko Makuta and Hidetoshi Murakami

Institute: Chuo University

Category: Simulation studies of random fields

Title: Simulation studies of random fields designed for brain image analysis

Abstract: Functional MRI (fMRI) provides spatial and temporal information about activated cortical regions without applying radioactive substances. We are interested in detecting the statistically significantly high intensity of the images which are interpreted as responding to the task events. For recognizing the regions of images corresponding to high intensity with task stimuli, the modeling of random fields plays an important role in giving tail probabilities. Classically adjustments of P-values are used to make regions by Bonferroni~Rs inequality. However, when we use Bonferroni~Rs inequality strictly, it is well-known that the specified P-value is too small and then almost very little regions are recognized. Gaussian random field modeling is recently used and the distribution of the maximum pixels controls FWER and also FDR. In this article we will simulated various Gaussian random fields with different spatial covariance structures and evaluate tail probabilities from the view point of the multiple comparisons. These simulations results show that the covariance structures of random fields and the smoothing may have much effect on tale probabilities.

Speaker: Kyung In Kim

Session FPM1-I: Large Scale Multiplicity Problems (II) (Friday, 1:30 PM-2:40 PM), Chair: Haiyan Xu

Co-Author: M. A. van de Wiel

Institute: Eindhoven University of Technology

Category: Bioinformatics/Genomics

Title: Estimating the FDR for interval null-hypotheses using nonparametric deconvolution

Abstract: Given a set of microarray data, the problem is to detect differentially expressed genes, using a False Discovery Rate (FDR) criterion to correct for multiple testing. As opposed to common procedures in literature, we do not base the selection criterion on statistical significance only, but also on biological significance. Therefore, we would like to select only those genes which are significantly more differentially expressed than some fold f (e.g. f=2). This corresponds to interval hypothesis testing (which uses inequality instead of equality in the null-hypothesis). Based on a simple error model, we discuss a naive estimator for FDR. We use the Bayesian interpretation of FDR: the probability that the parameter of interest lies in the null domain (e.g. mean log-ratio < 2) given that the test criterion exceeds a threshold. We show how to improve the simple estimator by using deconvolution. That is, we recover the density of the parameter of interest from the data and the (known) noise process. We study the performance of the method using simulations and apply it to real data.

Speaker: Koon-Shing Kwong

Session TAM2-I:Stepwise Test Procedures (Thursday, 10:30 AM-12:00 PM), Chair: Wei Liu

Co-Author: CHEUNG, Siu Hung

Institute: National University of Singapore

Category: Theory and foundations

Title: Stepwise multiple test procedures for the directional-mixed families

Abstract: Comparing several treatments with a control is a common objective in clinical studies. However, existing procedures mainly deal with particular families of inferences in which all hypotheses are either one- or two-sided. Recently, a single step procedure is proposed to cope with a more general testing environment in which the family of inferences is composed of a mixture of one- and two-sided hypotheses. Such families are called the directional-mixed families. In this paper, we propose the step-down and step-up multiple test procedures for testing such directional-mixed families. The performance of such stepwise procedures will be evaluated by a stimulation study of the average power of the tests.

Speaker: Christoph Lange

Session FPM1-II: Applications of MCPs to Genomic Problems (Friday, 1:30 PM-2:40 PM), Chair: Guohua Pan

Co-Author: Kristel van Steen

Institute: Harvard School of Public Health

Category: Bioinformatics/Genomics (Statistical Genetics)

Title: Genomic screening in family based association testing

Abstract: The Human Genome Project and its spin-offs such as the Allele Frequency/Genotype Project or the Haplotype Map Project are making it increasingly possible to disentangle the genetic basis of a given complex trait using genome-wide association studies. The statistical challenge in analyzing such genome-wide association studies stems from the severe multiple comparison problem that has to be dealt with. Standard multiple comparison methods are not likely to be successful in finding associations that achieve genome-wide significance. Our proposed methodology offers an alternative way to carry out genome-wide screenings in family-based association studies, while controlling the overall type I error rate.

Speaker: Øyvind Langsrud

Session TAM1-II: Applications of FDR to Microarray Data Analysis (Thursday, 8:30 AM-10:00 AM), Chair: Katie Pollard

Co-Author:

Institute: MATFORSK, Norwegian Food Research Institute.

Category: Normal theory, Multiple endpoints, Bioinformatics, Resampling based

Title: Adjusted p-values by rotation testing

Abstract: Rotation testing is a framework for doing exact significance testing under multivariate normality by using computer simulations (Langsrud, 2005). The classical generalizations of the univariate F statistic are independent of the unknown covariance matrix. But for other generalizations, the covariance matrix needs to be considered. Rotation testing handles this problem by conditioning on sufficient statistics. An important application is the adjustment of univariate p-values in multiresponse experiments according to the familywise error rate (FWE). Similar to how this problem is solved within the context of permutation testing, univariate F-test p-values in general linear models can be non-conservatively adjusted by using rotation testing. Within the field of genomics, such FWE adjustment can be viewed as being too strict and false discovery rate (FDR) methodology is often preferred. A property of the common FDR methods is that they do not make use of the dependence among the responses. However, as mentioned in Moen et al. (2005), an alternative is to compute a sort of FDR adjusted p-values by modifying the methodology for FWE adjustment. More specifically, the adjusted p-value for the n-th largest F-statistic (F[n]) is computed as the expected proportion of the n largest F statistics that exceeds our observed F[n]. This expectation is calculated under the rotation (or permutation) distribution. When n=1, this is equivalent to FWE adjustment. To enforce monotonicity these preliminary p-values are subjected to a step-up procedure. The methodology will be illustrated by a microarray example.

Speaker: Ning Li

Session WAM2-II: Multiplicity Issues in Clinical Trials (Wednesday, 10:30 AM-12:00 PM), Chair: Zhenming Shun

Co-Author: Yong-Cheng Wang, Lue Ping Zhao

Institute: US Food and Drug Adminstration

Category: Clinical trials(Nocology)

Title: A design methodology for evaluating oncology genomic studies with multiple comparisons issues

Abstract: Biomedical researchers begin adopting oncology genomic studies into drug development process to evaluate safety and efficacy of biopharmaceutical products. Because of significant costs, researchers often want to design studies carefully, maximizing the discovery power and minimizing the false positive discoveries (Type I errors). Among many frequently used designs, one of them is the two-group comparison study design, which involves a comparison between two groups, such as between cases and controls, or between tissue A and B. Evaluation of the study design, in traditional hypothesis testing framework, centers on the estimation of sample size, minimum detectable difference and power. When facing genomic studies with thousands of genes, we need to develop a new design methodology, appropriate for addressing genomewide significance and control the Type I error due to multiple comparison. In this presentation, we will describe a new design methodology for evaluation of oncology genomic studies. This methodology relies on a set of new design parameters, including number of false discoveries (NFD) and true discovery rate (TDR) that correspond to type I error rate and power, respectively. Based upon these design parameters, we introduce specific methods that are useful for

evaluating sample size, power and minimum detectable difference. Besides describing and justifying this method for evaluating study designs, this article also provides examples to illustrate its application.

Speaker: Susan Li

Session TPM1-I:Multiple Endpoints (Thursday, 1:30 PM-3:00 PM), Chair: Ajit Tamhane

Co-Author: Bill Wang, Ivan Chan

Institute: Merck & Co., Inc.

Category: Multiple endpoints problems

Title: A modified gatekeeping strategy and its application in testing multiple families of hypotheses in a clinical trial

Abstract: Gatekeeping strategies are increasingly being used in analysis of clinical trials to control the overall type I error when multiple endpoints/hypotheses are addressed. Based on this strategy, a primary family of hypotheses are treated as gatekeepers and tested first, and a secondary family of hypotheses is tested only if one or more gatekeeper hypotheses have been rejected. In this talk, we will first review gatekeeping strategies proposed in the literature; then we will present a modified gatekeeping method based on Hochberg~Rs step-up test. This proposed method has a weak control of error rate, and has a slightly inflated, yet acceptable, familywise error rate, especially under dependence of the endpoints. A simulation is also performed to study the error rate and power of this method when testing 2 and 3 families of hypotheses involving a mixture of continuous and categorical endpoints with a dependence structure. An example from a clinical trial will be used to illustrate the proposed method.

Speaker: Xiang Ling

Session TAM1-I: Applications of Partitioning Principle (Thursday, 8:30 AM-10:00 AM), Chair: Helmut Finner

Co-Author: Jason C. Hsu

Institute: The Ohio State University, Department of Statistics

Category: Designs (adaptive, optimal, sequential, etc.)

Title: Adaptive design of dose-response studies using the Partitioning Principle

Abstract: An adaptive two-stage design is proposed for dose-response studies to find the minimum effective dose. The procedure is conducted in a stepwise fashion based on the Partition Testing Principle with family wise error rate controlled strongly. We examine a wide dose range vs. a placebo in the first stage. Then an interim analysis is conducted with potential modification of design features of the experiment. Ineffective and/or unsafe dose treatments are terminated and selected doses are further investigated in the second stage. Inference is based on a pre-chosen conditional error function. Because of the stepwise method we used, our procedure allows different conditional error functions be applied to different doses. Several conditional error functions will be discussed, including a conditional error function that controls the maximum and minimum sample size.

Speaker: Jeen Liu

Session TPM1-II: Theoretical Aspects of MCPs (Thursday, 1:30 PM-3:00 PM), Chair: Jason C. Hsu

Co-Author: Chunzhang Wu, William Zhao

Institute: Astellas Pharmaceuticals US

Category: Clinical trials

Title: Power calculation for MCPs of three Binomials

Abstract: This work is motivated by a non-inferiority study comparing two doses of a test treatment to an active control arm where the primary efficacy endpoint is a binary outcome of treatment success. Let X, Y, Z be the number of treatment successes in each arm, with distributions Binom(N, Px), Binom(N, Py), Binom(N, Pz), respectively. We consider the multiple comparison problem of testing two hypotheses: H1: Px < Pz-D vs. Px >= Pz-D H2: Py < Pz-D vs. Py >= Pz ~VD where D is a pre-specified equivalence margin. Various MCPs controlling the overall type-I error are available. We consider three particular examples for illustration purpose, ~U Hochberg~Rs procedure based on separate tests for H1 and H2. ~U Testing the two hypotheses in a pre-specified order, e.g. testing H1 before H2. ~U An ad-hoc procedure by pre-testing H0: the pooled sample (X, Y) has a pooled rate of no less than Pz-D, before proceeding to test H1 and H2 separately. All individual tests of two Binomials are based on Chi-square test. An algorithm is proposed to compute the power functions of these procedures. The relative merits of these procedures

are then evaluated.

Speaker: Wei Liu

Session WPM2-I: MCPs in Regression Problems (Wednesday, 3:30 PM-5:00 PM), Chair: Juliet P. Shaffer

Co-Author:

Institute: Southampton University, UK

Category: Theory and foundations

Title: Regression analysis via confidence bands

Abstract: In regression analysis (Partial) F-test or Chi-square tests play a central role. We will point out the weeknesses of these tests and show how they can be improved by using simultaneous confidence bands.

Speaker: Jiandong Lu

Session FAM2-II: Dose Response Problems (Friday, 10:30 AM-12:00 PM), Chair: Xiaoyin Fan

Co-Author: Kim Hung Lo

Institute: Centocor, Inc

Category: Multiple endpoints problems

Title: Hierarchical testing procedures for the analysis of individual doses for clinical trials with multiple endpoints

Abstract: In confirmatory clinical trials, primary and secondary endpoints are tested. When the secondary endpoint(s) is an integral part of the regulatory claim or can be used for an additional claim, it is critically important to prospectively specify the strategies for dealing with multiplicity problems. Hierarchical testing procedures are often used in such context. In this article, we discuss several methods of constructing the testing procedure when more than one dose of an experimental drug is tested. Given the need for the strongly control of family wise type I error, the hierarchical structure of the testing procedure for multiple endpoints and multiple treatment comparisons becomes unsettled. We propose a hierarchical structure within each treatment comparison provided overall test for the primary endpoint is significant. The proposed hierarchical testing procedure will be illustrated using an example from a dose finding study with multiple endpoints. The power under various alternative hypotheses is compared with competing methods via simulation studies.

Speaker: Vered Madar

Session TPM1-II: Theoretical Aspects of MCPs (Thursday, 1:30 PM-3:00 PM), Chair: Jason C. Hsu

Co-Author:

Institute: Tel-Aviv University, Israel

Category: Multiple endpoints problems

Title: Simultaneous confidence intervals for multiple parameters with more power to determine the sign

Abstract: We offer new simultaneous two-sided confidence intervals for the estimation of the expectations of k normal random variables. A family of especially designed nonsymmetric rectangular acceptance regions is inverted into a confidence set. The convex-hull of the confidence set is then projected onto the coordinate axes to form new confidence intervals. Besides offering coverage, the new intervals also provide stronger sign classification for each expectation than the sign classification offered by the conventional two-sided intervals. As a trade off, the new intervals are nonequivariant; their lengths might grow as the sample point approaches the coordinate axes, while for many other situations the new intervals coincide with the conventional ones.

Speaker: Willi Maurer

Session TPM2-II: Adaptive Designs (Thursday, 3:30 PM-4:40 PM), Chair: Steve Sun

Co-Author: Frank Bretz, Heinz Schmidli

Institute: Novartis Pharma AG

Category: Designs (adaptive, optimal, sequential, etc.)

Title: Confirmatory seamless phase II/III clinical trials with treatment selection at interim

Abstract: Classical drug development consists of a sequence of independent trials in different phases. In a typical phase II trial one would compare several treatments (for example, different dose levels of a new compound) with a control. After the completion of this trial it is then decided, whether or how to continue the drug development and which treatment(s) to carry forward to the phase III. The phase III trials are then evaluated as stand-alone confirmatory trials, ignoring information from previous phases. Adaptive seamless designs aim at interweaving these trials by combining them into one single study conducted in two (or more) stages. In the example above, one (or more) treatment is selected after the first stage based on the available data at interim, and investigated further in the second stage. The final analysis of the selected treatment includes the patients of both stages and is performed such that the overall type I error rate is controlled at pre-specified level. Ideally, adaptive seamless designs thus (i) reduce the intermediate decision time, (ii) save costs through the need for less patients or have increased overall power, and (iii) get long-term safety data earlier. In this talk we review the major underlying statistical techniques. We introduce a clinical example, describe the experiences obtained from designing a combined phase II/III clinical trial and discuss advantages and disadvantages and hurdles associated with such an approach.

Speaker: Tetsuhisa Miwa

Session FAM1-II:Isotonic Inference Problems (Friday, 8:30 AM-10:00 AM), Chair: Frank Bretz

Co-Author: A. J. Hayter and Satoshi Kuriki

Institute: National Institute for Agro-Environmental Sciences

Category: Computing

Title: The evaluation of normal orthant probabilities with singular correlation matrices

Abstract: Miwa et al. (JRSSB, Vol. 65, 2003) showed how non-centred orthant probabilities with non-singular correlation matrices are calculated accurately by expressing them as differences of a finite number of orthoscheme probabilities. They also provided an effective procedure to evaluate non-centred orthoscheme probabilities. However, it was essential in their method that the correlation matrix should be non-singular. In this paper we present a procedure to evaluate orthant probabilities with any singular correlation matrices. The procedure is based on the dissectioning of a polyhedron into non-singular polyhedral cones.

Speaker: Tomohiro Nakamura

Session FAM2-I: Change Point and Selection Problems (Friday, 10:30 AM-12:00 PM), Chair: Jie Chen

Co-Author: Douke Hideyuki, Ujiie Katsumi

Institute: Tokai University

Category: Designs (adaptive, optimal, sequential, etc.)

Title: Group sequential procedure to find the changing population mean

Abstract: In this study, we discuss a group sequential procedure to find a stage wherein the sequence of population means is changed at some stage. In this procedure, we adopt t statistic to compare sequentially a specified population mean with each of other population means. To realize the procedure, we deal with the repeated confidence boundaries based on Armitage's method(1969) in the repeated significance test.

Speaker: Jianan Peng

Session FAM2-I: Change Point and Selection Problems (Friday, 10:30 AM-12:00 PM), Chair: Jie Chen

Co-Author: Chu-In Charles Lee, Hubert J. Chen

Institute: Acadia University

Category: Screening and selection

Title: A new approach to subset selection for normal treatments

Abstract: A subset selection procedure is developed for the problem of selecting the treatment with the largest mean for k normal treatments with common variance. The procedure is based on union-intersection test and isotonic regression. The results of a simulation study comparing the new procedure with Gupta~Rs procedure are present. A real data example is given to illustrate the procedure.

Speaker: Gene Pennello

Session FAM1-I: Bayesian MCPs (Friday, 8:30 AM-10:00 AM), Chair: Peter Westfall

Co-Author:

Institute: US Food and Drug Adminstration

Category: Bayesian Methods, Decision Theory, or Theory and Foundation

Title: Bayes rule multiple comparison procedures: A simpler life

Abstract: In this talk, we argue that the Bayesian decision-analysis approach to multiple comparison problems can be simpler, more natural, more logical, more scientific, and more illuminating than the frequentist approach of controlling familywise Type I error rate. We show that the frequentist approach has logical difficulties even for a single comparison and for simultaneous non-inferiority/superiority testing. We show that the joint Bayes rule for multiple comparisons is simple if the joint decision loss is defined as the sum of the decision losses for the component testing problem: it is the simultaneous application to each component problem of the Bayes rule for that problem considered alone. In other words, under additive losses the optimal approach is comparisonwise, that is, does not depend the number of component tests, unlike the frequentist approach. By assuming exchangeability among related comparisons in the prior distribution, a joint Bayes rule can be argued to be more scientific than the frequentist approach, which only considers familywise control of the Type I error rate, a purely statistical construct. k-Ratio joint Bayes rules (cf. Duncan and Dixon, 1983), which assume additive losses and exchangeability, are illustrated for such problems as comparisons of one-way and two-way means, comparisons of treatments vs. controls, comparisons within subgroups, and subset selection.

Speaker: Gene Pennello

Session WPM2-II:Clinical Trial Applications (Wednesday, 3:30 PM-5:00 PM), Chair: A. Lawrence Gould

Co-Author:

Institute: US Food and Drug Adminstration

Category: Bayesian methods or Regulatory Affairs or Designs (sequential)

Title: Approximate sequential Bayes rules for clinical trials submitted to the US FDA

Abstract: Sequential Bayes Rules stop at an interim stage when the posterior Bayes risk is less than the minimum expected posterior Bayes risk over all larger sample sizes. Even in today~Rs computing environment, computation of sequential Bayes rules can be difficult, requiring complex dynamic programming. Moreover, sequential Bayes rules can be problematic for clinical trials submitted to FDA because they depend on a definition of the cost per observation, which FDA cannot consider in evaluating a medical product for safety and effectiveness. We present approximate sequential Bayes rules that are easy to compute and avoid defining the cost per observation explicitly. First, the end stage sample size is determined (e.g., through agreement with FDA). The end stage sample size implicitly defines the cost per observation as the difference between the Bayes risk at the end stage and the Bayes risk at the end stage plus one more observation. Second, stopping at an interim stage is based on keeping the Bayes risk the same as at the end stage. This criterion is similar to the Bayes rule criterion of maintaining the same minimum posterior Bayes risk and therefore should be a decent approximation to the Bayes rule. To make the stopping criterion acceptable to FDA, the Bayes risks can be computed by setting the cost per observation to zero and only considering costs of decision errors. At each interim stage, critical z values a and b are determined such that (1) if $z < a$ the trial is stopped and the null hypothesis is accepted, (2) if $b > a$ the trial is stopped and the null hypothesis is rejected, and (3) if $a < z < b$, the trial continues. As the trial continues to the end stage, a and b converge to the same value c. Computation of a and b is remarkably easy and involves equating the posterior odds of the null at the end stage to that at the interim stage. For simple vs. simple hypotheses with equal prior probabilities, computation of a and b involves equating likelihood ratios.

Speaker: Katherine Pollard

Session WAM2-I: MCPs in Microarray Data Analysis (Wednesday, 10:30 AM-12:00 PM), Chair: Gene Pennello

Co-Author: Patricia Chan, Todd M. Lowe, David Hinds, Krishna Pant, Merrill D. Birkner, Sandrine Dudoit, Mark J. van der Laan

Institute: University of California, Santa Cruz

Category: Bioinformatics/Genomics If others: resampling-based methods, theory and foundations

Title: Genomic applications of new multiple testing procedures based on a test statistics null distribution

Abstract: Center for Biomolecular Science & Engineering, University of California, Santa Cruz References: http://lowelab.ucsc.edu/katie Co-authors: Patricia Chan, Todd M. Lowe, David Hinds, Krishna Pant, Merrill

D. Birkner, Sandrine Dudoit, and Mark J. van der Laan Multiple testing problems arise whenever one wishes to perform statistical tests for each of many genes or genomic regions. We have proposed resampling-based multiple testing procedures (MTP) for controlling a broad class of Type I error rates defined as tail probabilities for arbitrary functions of the numbers of Type I errors and rejected hypotheses. A key component of these new single-step and stepwise MTPs is the characterization of the null distribution used to do multiple testing (ie: to compute rejection regions, confidence intervals and p-values). Our approach is novel, because it utilizes the null distribution of the test statistics directly - rather than deriving it from a data generating null distribution - and hence does not require the subset pivotality condition. Therefore, researchers can now perform genome-wide tests involving general data generating distributions, null hypotheses, and test statistics, including some problems which are not covered by existing methods. Among these are tests involving pairwise correlations and association parameters in non-linear models. The proposed MTPs have been applied to a number of interesting problems in human and microbial genomics: (i) Are microarray expression profiles of genes predicted to be in the same mRNA transcript (operons) in fact correlated? (ii) Which DNA sequence variants are associated in human populations with a clinical outcome (eg: survival) based on data from a whole-genome genotyping array? (iii) Are specific codon positions associated with HIV-1 viral replication capacity? The open-source software package multtest (www.bioconductor.org) implements the proposed MTPs, including resampling procedures which provide consistent estimators of the test statistics null distribution.

Speaker: Martin Posch

Session TAM2-II:Large Scale Multiplicity Problems (I) (Thursday, 10:30 AM-12:00 PM), Chair: Wenjin Wang

Co-Author: Sonja Zehetmayer and Peter Bauer

Institute: Medical University of Vienna

Category: Designs (adaptive, optimal, sequential, etc.)

Title: Two-stage designs for experiments with a large number of hypotheses

Abstract: We deal with the situation that a large number of hypotheses is investigated and sampling costs are constrained. Instead of distributing the sample size over the hypotheses in a single-stage design, a two-stage design is considered: The first stage is used to screen the "promising" hypotheses which are then further investigated at the second stage. A multiple one-sided test procedure is proposed which aims at the control of the false discovery rate. It is based on individual p-values appropriately defined for the two-stage design and explicitly worked out for the case of independent normally distributed test statistics with known variances. Asymptotically optimal designs are derived depending on the number of null hypotheses, the total costs, the proportion of true null hypotheses and a common effect size under the alternative. It can be shown, that the power of the two-stage design is impressively larger than the power of the corresponding single-stage design with equal costs. Optimal designs can also be derived when sampling costs differ between stages. Extensions for the case of unknown variances, distributed effect sizes under the alternatives, correlated test statistics and the two-sided test are investigated by simulations. Moreover, it is shown that the simple multiple test procedure using first stage data only for screening purposes and deriving the test decisions only from second stage data is an option which considerably outperforms conventional single-stage tests.

Speaker: Hui Quan

Session WAM2-II: Multiplicity Issues in Clinical Trials (Wednesday, 10:30 AM-12:00 PM), Chair: Zhenming Shun

Co-Author: Tom Capizzi, Ji Zhang

Institute: Merck Research Laboratories

Category: Clinical trials

Title: Multiplicity adjustment for clinical trials with two doses of an active treatment and multiple primary and secondary endpoints

Abstract: Frequently, two doses of an active treatment and multiple primary and secondary endpoints are simultaneously considered in Phase III confirmatory clinical trials. For these trials, many traditional multiplicity adjustment procedures do not take into account the possible dose effect on each endpoint and the priority order of the primary and secondary endpoints, and therefore may have lower power. To gain power, in this paper, we consider the problem as a three-dimensional multiplicity problem: one dimension concerns the multiple doses, one dimension concerns the priority order of the primary and secondary endpoints and another dimensional concerns the multiple endpoints in each priority category. We propose procedures that consider the dose order and the priority of the endpoints to form the closure of the procedures and therefore control the family-wise error rate. Furthermore, we consider procedures that provide control of type I error rates in clinically relevant sub-families of comparisons, providing a

pragmatic approach to maintain study power as compared to traditional ultra conservative approaches for overall strong control. Numerical examples and real data example show that the procedures proposed in this paper in general are easy to use and have improved power.

Speaker: Anat Reiner

Session TAM1-II: Applications of FDR to Microarray Data Analysis (Thursday, 8:30 AM-10:00 AM), Chair: Katie Pollard

Co-Author: Yoav Benjamini, Greg Elmer, Daniel Yekutieli

Institute: Tel-Aviv University, Israel

Category: Bioinformatics/Genomics

Title: Complexity of data and analysis related to FDR control in microarray experiments

Abstract: Statistical issues involved in the analysis of gene expression data are of relevance for many other types of data. Frequently confronted problems are related both to the data itself and the analytical process. I will discuss them through the aspect of controlling type I error, specifically the false discovery rate (FDR), as the problem of multiple testing is of immediate concern once a large set of genes is analyzed. I will take a look at the behavior of FDR attributed to the fact that microarray data is typically subjected to technological and biological factors that are potential causes of dependencies. I will examine more closely the case of two-sided tests, which is highly encountered but problematic when some of the null hypotheses are false. A few scenarios of dependency structure will be represented along with the respective least favorable cases. In addition, the control of the FDR is complicated when conducting a more complex analysis, such as pairwise comparisons and interaction contrasts, on a gene level. Furthermore, correlation analysis may be used when incorporating additional biological measures with the genetic expression data, for the purpose of exploring the relations between them. In these cases, rather then testing all null hypothesis directly, we may prefer to split the statistical analysis route into several main research questions, or stages, possibly in hierarchical manner, and control the FDR for each research direction separately. I will present a functional genomic research application along with simulations results.

Speaker: Sanat Sarkar

Session TPM2-I: Advances in False Discovery Rate (II) (Thursday, 3:30 PM-4:40 PM), Chair: Daniel Yekutieli

Co-Author:

Institute: Temple University

Category: False Discovery Rate

Title: Two-stage FDR procedures

Abstract: A class of two-stage step-up procedures is defined. Explicit formula for the FDR of such a procedure is derived under any distributional setting before determining critical values that provide a control of FDR under independence. A newer class of modified Benjamini-Hochberg procedures, including the one given in Storey, Taylor and Siegmund (2004}, are obtained.

Speaker: Juliet Shaffer

Session TPM1-II: Theoretical Aspects of MCPs (Thursday, 1:30 PM-3:00 PM), Chair: Jason C. Hsu

Co-Author:

Institute: University of California, Berkeley

Category: Theory and foundations

Title: Multiple requirements for multiple test procedures

Abstract: A number of different error rate criteria for multiple testing have been proposed within the last few years, each in isolation. Concerns have been raised in the literature about problems with some of the criteria. For example, control of the g-FWER or k-FWER has been proposed recently; this is control of the probability of k or more Type I errors with designated probability alpha. This criterion, in isolation, allows k-1 declarations of significant effects with no requirements on the associated p-values, not even any ordering. Although there have been occasional additional stipulations, there apparently hasn't been any formal treatment of this issue. The talk will discuss possible added requirements for the k-FWER and other criteria, will note some past discussions related to the issue of additional desirable properties of procedures, and will give examples of the application of multiple criteria.

Speaker: Zhenming Shun

Session WAM2-II: Multiplicity Issues in Clinical Trials (Wednesday, 10:30 AM-12:00 PM), Chair: Zhenming Shun

Co-Author: Chi, Sylvain Durrleman, Lloyd Fisher

Institute: Sanofi-Aventis

Category: Clinical trials(Multiplicity)

Title: Statistical consideration of the strategy for demonstrating clinical evidence of effectiveness ~W one larger vs two smaller pivotal studies

Abstract: As a regulatory strategy, it is nowadays not uncommon to conduct one confirmatory pivotal clinical trial, instead of two, to demonstrate efficacy and safety in drug development. This paper is intended to investigate the statistical foundation of such an approach. The one-study approach is compared with the conventional two-study approach in terms of power, type-I error, and fundamental statistical assumptions. Necessary requirements for a single-study model is provided in order to maintain equivalent evidence as that from a two-study model. In general, one-study model is valid only under a ~Sone population~T assumption. In addition, higher data quality and more convincing and robust results need to be demonstrated in such cases. However, when ~Sone-population~T assumption is valid and appropriate methods are selected, a one-study model can have a better power using the same sample size. The paper also investigates statistical assumptions and methods for making an overall inference when a two-study model has been used. The methods for integrated analysis are evaluated. It is important for statisticians to select correct pooling strategy based on the project objective and statistical hypothesis.

Speaker: Paul Somerville

Session WPM1-I:Advances in False Discovery Rate (I) (Wednesday, 1:30 PM-3:00 PM), Chair: Yoav Benjamini

Co-Author: Claudia Hemmelmann, University of Jena

Institute: University of Central Florida

Category: Normal theory, linear/non-linear models

Title: FDR procedures controlling the number and proportion of false positives

Abstract: FDR procedures are developed which control the number and proportion of false positives with a given probability. The procedures use a "reduced step FDR" or a "truncation" of the FDR procedure by specifying the number of steps, and, in effect, specifying minimum critical values (MCV's). The distribution of the test statistics is assumed to be multivariate-t, with a common correlation r. Existing tables for r = 0, .1 and .5, n = 15 and ¥, and a select number of hypotheses ranging from 50 to 10,000, are utilized. Tables are produced for procedures which maximize power while controlling the number of false positives. An example is given and results are compared with a previously published work using step-wise permutation based methods. Previously published tables giving critical values for test statistics are converted to critical p-values. It is hoped that the tables may be useful when the assumption of a multivariate-t distribution is not valid.

Speaker: Klaus Strassburger

Session TAM1-I: Applications of Partitioning Principle (Thursday, 8:30 AM-10:00 AM), Chair: Helmut Finner

Co-Author: Frank Bretz, Helmut Finner

Institute: German Diabetes Center, Institute of Biometrics & Epidemiology

Category: Closed testing and partitioning principle

Title: Improved fixed ordered testing procedures based on the partitioning principle

Abstract: In the first part of the talk we illustrate the basic idea behind the partitioning principle. It will be demonstrated how to implement the partitioning technique in order to improve multiple tests for a preordered family of hypotheses. In the second part we tackle the problem of multiple comparisons with the best (MCB) assuming an order relation among treatments. In practice such relations often occur quite naturally. Treatments may be ordered according to some cost measure such as the financial expense of the treatment, the amount of the treatment's side effects, or some other secondary criteria. We investigate the problem of detecting the treatment with lowest cost among all those treatments, which are in some sense equivalent to the most effective (best) treatment. Among others, we derive a lower confidence bound for the index corresponding to the treatment of interest. It will be shown that the proposed fixed sequence tests provide improved confidence bounds compared with competing testing strategies.

Speaker: Steven Sun

Session WPM2-II:Clinical Trial Applications (Wednesday, 3:30 PM-5:00 PM), Chair: A. Lawrence Gould

Co-Author:

Institute: Johnson & Johnson PRD

Category: Clinical trials

Title: Adjusted p-values for multiple testing of significance in clinical trials

Abstract: ICH guideline calls for multiplicity adjustment when multiple primary endpoints are present in clinical trials. Even if a trial has one primary efficacy endpoint only, it usually involves multiple secondary endpoints. Adjustment for multiplicity is still required if supportive secondary endpoints need to be included in the label. In this talk, different modified Bonferroni testing procedures such as Holm^Òs, Hochberg^Òs and Hommel^Òs procedures will be reviewed and contrasted. Comparison of modified Bonferroni testing procedures with re-sampling based testing procedures will be made. Strategies for multiplicity adjustment in the design phase will be discussed. Finally, A detailed example will be used to illustrate the importance of adjustment procedure selection.

Speaker: James Troendle

Session WPM1-II: Analysis of Safety Data (Wednesday, 1:30 PM-3:00 PM), Chair: Willi Maurer

Co-Author:

Institute: National Institutes of Health

Category: Resampling-based methods (bootstrap, MCMC, etc.)

Title: Testing multiple Bernoulli outcomes with covariates

Abstract: The problem of adjusting for multiplicity when one has multiple outcome variables can be handled quite nicely by step-down permutation tests. More difficult is the problem when one wants an analysis of each outcome variable to be adjusted for some covariates and the outcome variables are Bernoulli. Special permutations can be used where the outcome vectors are permuted within each strata of the data defined by the levels of the (made discrete) covariates. This method is described and shown to control the familywise error rate at any prespecified level. The method is compared through simulation to a Vector Bootstrap approach, also using a step-down testing procedure. It is seen that the method using permutations within strata is superior to the Vector Bootstrap in terms of error control and power. The method is illustrated on a dataset of 55 minor malformations of babies of diabetic and non-diabetic mothers.

Speaker: Weizhen Wang

Session TAM2-I:Stepwise Test Procedures (Thursday, 10:30 AM-12:00 PM), Chair: Wei Liu

Co-Author: Daniel T. Voss

Institute: Wright State University

Category: Closed testing and partitioning principle

Title: Step-down tests procedures in orthogonal saturated designs

Abstract: In orthogonal saturated designs, the number of observations is equal to the number of effects and then there is no variance estimator that is independent of the effect estimators. The primary interest is to identify nonzero effects without knowing how many and which effects are nonzero. Using data to decide the number of effects to estimate the variance (so called adaptive procedure) is certainly desirable. In this talk, we provide two step-down tests procedures to identify nonzero effects. Both procedures are adaptive and strongly control the experimentwise error rates. One include as special cases the individual nonadaptive tests of Berk and Picard (1991) and the simultaneous nonadaptive tests of Voss (1988). The other generalizes the result of Holm, Mark and Adolfsson (2005) test and obtains a large class of iterative step-down tests.

Speaker: Yong-Cheng Wang

Session WAM2-II: Multiplicity Issues in Clinical Trials (Wednesday, 10:30 AM-12:00 PM), Chair: Zhenming Shun

Co-Author: Ning Li

Institute: US Food and Drug Adminstration

Category: Clinical trials(Oncology)

Title: Multiplicity issues in oncology mortality trial with treatment crossover

Abstract: Patients who switch treatment groups (treatment crossover) in randomized oncology trials can cause problems in the statistical design, data analysis and interpretation of the results, because the original randomized manner may be changed to a non-randomized manner. These changes can result in treatment effects of the treatment groups to be more similar. It also involves multiplicity issues in the usual sensitivity analyses. Smith et al. [1997] proposed a generalized linear model that is based on the proportional hazard model and extends Efron's survival model for the interval censored survival data. We propose an extended model based on the different estimation for the baseline hazard function and apply the model to the survival data with treatment crossover. Based on our extended model, it avoids the multiplicity issues.

Speaker: Peter Westfall

Session TAM2-II: Large Scale Multiplicity Problems (I) (Thursday, 10:30 AM-12:00 PM), Chair: Wenjin Wang

Co-Author:

Institute: Texas Tech University

Category: Decision theory

Title: Optimal data snooping: Is Bonferroni admissible for large k?

Abstract: Modern methods of multiple comparisons, including FDR-controlling, Bayesian, and decision-theoretic, are lax relative to the Bonferroni method in their assignment of significances; they are relatively more lax as k, the number of tests, increases. I point out that this laxness is based on an assumption concerning the size of the loss due to Type I errors relative to loss due to Type II errors. I challenge the generality of this assumption, and present an alternative loss function for which the Bonferroni method is appropriate. Using examples, I demonstrate that the proposed loss function is reasonable and applicable to data snooping and data mining, and that it can provide better decisions.

Speaker: Keith Worsley

Session FPM1-I: Large Scale Multiplicity Problems (II) (Friday, 1:30 PM-2:40 PM), Chair: Haiyan Xu

Co-Author: Jonathan Taylor, Stanford

Institute: McGill University

Category: Theory and foundations

Title: Giant multiple comparison problems with random field data in brain mapping and 'bubbles'

Abstract: Giant multiple comparison problems occur frequently in brain mapping. A good example is the comparison of data at all pairs of locations in a series of 3D images from fMRI, where the number of comparisons is 40,000 x 40,000. We are interested in detecting those pairs of points that have highly correlated data values, suggesting functional connectivity. The problem is to find a suitable threshold to control the P-value. The theoretical challenge is that the 3D images are smooth random fields. We use methods from differential geometry and Morse theory to find extremely accurate approximations. However when the random fields are discretely sampled, the Bonferroni is a very good competitor. We present results on a new improved Bonferroni-type bound based on discrete local maxima (DLM) that is better than either method. These methods could be useful for any type of multiple comparison problem where there is some temporal or spatial structure to the data. We give applications to various types of brain mapping data, and to the new `bubbles' technique for detecting areas of the face used to discriminate fear from happiness.

Speaker: Lang Wu

Session TPM1-I:Multiple Endpoints (Thursday, 1:30 PM-3:00 PM), Chair: Ajit Tamhane

Co-Author: Michael D. Perlman

Institute: University of British Columbia, Canada

Category: Theory and foundations

Title: Some improved tests for multivariate one-sided hypotheses

Abstract: Multivariate one-sided hypothesis-testing problems are very common in clinical trials with

multiple endpoints. The likelihood ratio test (LRT) and union-intersection test (UIT) are widely used for testing such problems. It is argued that, for many important multivariate one-sided testing problems, the LRT and UIT fail to adapt to the presence of subregions of varying dimensionalities on the boundary of the null parameter space and thus give undesirable results. Several improved tests are proposed that do adapt to the varying dimensionalities and hence reflect the evidence provided by the data more accurately than the LRT and UIT. The methods are applied to real data examples. (This is a joint work with Professor Michael Perlman.)

Speaker: Samuel Wu

Session TAM2-I:Stepwise Test Procedures (Thursday, 10:30 AM-12:00 PM), Chair: Wei Liu

Co-Author: Weizhen Wang

Institute: University of Florida

Category: Theory and foundations

Title: Step-up simultaneous tests

Abstract: Step-up Simultaneous Tests for Identifying Active Effects in Orthogonal Saturated Designs A sequence of null hypotheses regarding the number of negligible effects (zero effects) in orthogonal saturated designs is formulated. Two step-up simultaneous testing procedures are proposed to identify active effects (nonzero effects) under the commonly used assumption of effect sparsity. It is shown that each procedure controls the experimentwise error rate at a given α level in the strong sense.

Speaker: Haiyan Xu

Session TAM1-I: Applications of Partitioning Principle (Thursday, 8:30 AM-10:00 AM), Chair: Helmut Finner

Co-Author: Jason Hsu

Institute: The Ohio State University, Department of Statistics

Category: Closed testing and partitioning principle

Title: Using the Partitioning Principle to control generalized Familywise Error Rate

Abstract: In some situations of testing multiple hypotheses, the loss function is roughly proportional to the number of false rejections. For such situations, controlling the generalized familywise error rate (gFWER), which is the probability of making more than m (³0) false inferences, is appropriate. Traditional familywise error rate (FWER) is the special case of gFWER with m = 0. We propose the generalized Partitioning Principle for constructing gFWER-controlling multiple tests. As is the case with using the Partitioning Principle to construct FWER-controlling methods, an advantage of using our principle is the ability to take into account the joint distribution of test statistics. How gFWER depends on this joint distribution is surprisingly different from how FWER depends on the distribution. We use the generalized Partitioning Principle to construct modeling-based stepdown tests which control gFWER. As an application, we use these methods to analyze gene expression levels from microarray experiments.

Speaker: Yoshiro Yamamoto

Session FAM1-II:Isotonic Inference Problems (Friday, 8:30 AM-10:00 AM), Chair: Frank Bretz

Co-Author:

Institute: Tokai University

Category: Theory and foundations

Title: An optimum linear test statistic of the homogeneity against the simple loop order on a (p, q) array

Abstract: The multivariate analogue of the one sides test with singular covariance matrix is difficult to perform. Thus Shi and Kudo (1987) and Shi (1987) gave a necessary and sufficient condition for a vector to provide an optimum linear test. In this paper, we provide the set of coefficients for an optimum contrast test statistic for testing homogeneity against the loop order alterative on (p,q) array.

Speaker: Brian Yan

Session FAM2-II: Dose Response Problems (Friday, 10:30 AM-12:00 PM), Chair: Xiaoyin Fan

Co-Author:

Institute: Shire Pharmaceutical Development

Category: Clinical trials

Title: Multiple tests for comparison of several doses with a zero-dose control

Abstract: In a clinical trial involving comparison of several doses with a control, the objective is to find effective doses when they are compared to a placebo. Several testing procedures could be used to assess the effectiveness of the active doses. Multiple tests with control of the familywise error, including Dunnett~Rs test, Williams~R test and Tamhane~Rs step-down or step-up procedure are discussed. These testing procedures are evaluated and compared using the Monte Carlo method.

Speaker: Daniel Yekutieli

Session WPM1-I:Advances in False Discovery Rate (I) (Wednesday, 1:30 PM-3:00 PM), Chair: Yoav Benjamini

Co-Author: Yoav Benjamini

Institute: Tel-Aviv University, Israel

Category: Error rates

Title: Hierarchical False Discovery Rate controlling procedures

Abstract: The False Discovery Rate approach has been successfully used in many applications. Even though the statistical methods employed are very sophisticated and the amount of data analyzed is formidable, the task performed is simple: simultaneously test a family of hypotheses, determined in advance, while controlling the expected proportion of false discoveries. In my talk I will introduce the result of joint work with Yoav Benjamini - FDR trees, a class of hierarchical FDR controlling procedures. FDR trees can perform complex statistical analysis and are generally more powerful than single-stage FDR methods. I will present the theoretical properties of FDR trees, compare FDR trees to existing methods of multiple testing, then demonstrate the great flexibility of FDR trees with real data examples.

Speaker: Ying Zhang

Session WPM2-I: MCPs in Regression Problems (Wednesday, 3:30 PM-5:00 PM), Chair: Juliet P. Shaffer

Co-Author: Wei Liu, Motaza Jamshidian

Institute: University of Iowa

Category: Normal theory, linear/non-linear models

Title: A simple multiple comparison procedure for linear regression lines

Abstract: A simulation-based multiple comparison procedure for linear regression lines is proposed. This procedure extends the method proposed by Spurrier (1999) by allowing different design matrices for the different regression lines and allowing each independent variable constrained in a bounded interval. Although the distribution of the test statistic is hard to derive analytically, an easy-to-implement Monte-Carlo simulation method is devised to carry out the comparison procedure. The method is demonstrated by the application in merging batches of drugs for estimating the drug shelf life.

Speaker: Bei Zhou

Session FAM2-II: Dose Response Problems (Friday, 10:30 AM-12:00 PM), Chair: Xiaoyin Fan

Co-Author:

Institute: Johnson and Johnson (Centocor)

Category: Clinical trials

Title: Multiplicity adjustments for clinical trials with 2 doses for an active treatment and a placebo control

Abstract: In phase III clinical trials, it is very common to have 2 doses of an active treatment and a placebo control. These two doses may have very similar treatment effects. For these trials, traditional multiplicity adjustment procedures such as Bonferroni and Hochberg can be used to control the family-wise type I error rate. However, these approaches may have lower power in some situations. The traditional methods will be compared to a method with simple ~Qgate-keeping~R test controlling the family wise error. Examples and simulations will be provided for binary and continues endpoints.

Speaker: Tianhui Zhou

Session WPM1-I:Advances in False Discovery Rate (I) (Wednesday, 1:30 PM-3:00

PM), Chair: Yoav Benjamini

Co-Author: Sanat Sarkar

Institute: Temple University

Category: Bayesian methods

Title: Bayes False Discovery and False Non-Discovery Rates

Abstract: Bayesian theories of false discoveries and false non-discoveries in multiple testing are developed based on a decision theoretic formulation that allows defining measures of false discoveries and false non-discoveries in terms of either randomized or non-randomized decisions on the null hypotheses. Bayes false discovery rate (BFDR) procedures are constructed through controlling posterior false discovery rate (PFDR) and compared with Benjamini-Hochberg and Efron~Rs Bayesian FDR procedures in terms of Bayes false non-discovery rate (BFNR).