East Asia Regional Biometric Conference 2007

Abstract Book

9-11 December 2007
University of Tokyo, Japan

This conference is organaized by
The Biometric Society of Japan
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Notes for Presenters

Oral Session

Please come to the Ichijo Hall at least 10 minutes before your session's starting time and meet with your chairperson, who is supposed to confirm all speakers of the session.

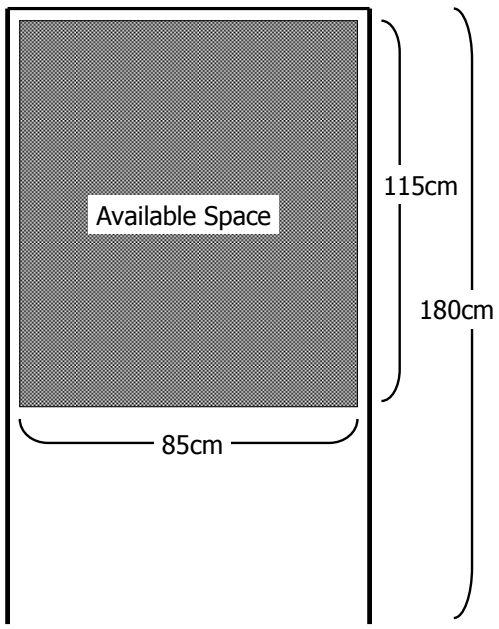
An LCD projector is available for presentation. Notebook computers can be connected to analog RGB interfaces.

Instructions for Speakers in Oral Sessions

- Oral presentations are scheduled so that each speaker will have at least 15 minutes.
- An LCD projector can be used. If you would like to use OHP, please contact with EAR-BC'07 staff.
- Your own notebook computer can be connected to an LCD projector which has an analog RGB interface (DSUB15).
- If you don't bring a notebook computer, please contact with EAR-BC'07 staff members. Please prepare your presentation file which can work on Microsoft PowerPoint 97-2003.

Poster Session

Posters will be on display at the lobby of the conference venue. Posters may be mounted on the morning of December 9th (at or before the coffee break). Your poster has been assigned a specific "poster number" that corresponds to a specific portion of a poster board.
Your poster is to be displayed for 2 days. In order to ensure that those who wish to discuss it with you have a chance to do so, it is highly recommended that you be at your poster during each of the scheduled coffee breaks.
Posters must be removed by 17:00 on December 10th.



Instructions for Presenters in Poster Session
Available space for each poster is: Width 85cm and Height 115cm.

Programme over view

Sunday,9th

8:30-	Registration
8:55-9:00	Opening Address *Toshiro Tango,* Japanese Region President
9:00-10:30	Opening Ceremony: Introduction to IBS and its regional activities (O:01-05) Chair: *Ashwini Mathur*
	Coffee Break
11:00-12:30	Invited Session: Clinical Trials (I:01-03) Chair. *Shigeyuki Matsui*
	Lunch Break
14:00-15:30	Contributed Session: Epidemiology (C:01-04) Chair: *Yutaka Matsuyama*
	Coffee Break
16:00-17:30	Contributed Session: Bioinformatics (C:05-09) Chair: *Seiya Imoto*

Monday,10th

8:30-	Registration
9:00-10:30	Invited Session: Bioinformatics (I:04-06) Chair: *Masaaki Matsuura*
	Coffee Break
11:00-12:00	Keynote Lecture (K:01) Chair: *Thomas Louis*
	Lunch Break
13:30-15:00	Invited Session: Epidemiology (I:07-09) Chair: *Tosiya Sato*
	Coffee Break
15:30-17:00	Contributed Session: Clinical Trials 1 (C:10-13) Chair: *Satoshi Morita*
17:30-	Conference Dinner at Capo PELLICANO

Tuseday,11th

8:30-	Registration
9:00-10:30	Contributed Session: Biostatistics in General (C:14-17) Chair: *Shizue Izumi*
	Coffee Break
11:00-12:30	Contributed Session: Clinical Trails 2 (C:18-21) Chair: *Osamu Komiyama*
12:30-12:35	Closing Remarks *Tosiya Sato,* Scientific Programme Chair

Sunday,9th-Monday,10th

9:00-17:00	Poster Session

Other Activities

Tuseday,11th

13:30-17:00	Biometric Seminar (Sponsored by Japanese Biometric Society)

Scientific Programme

Opening Ceremony: Introduction to IBS and its regional activities

Chair: *Ashwini Mathur* (the IBS General Secretary, Indian Region)

Sunday,9th 9:00-10:30	*Thomas Louis* (the IBS President, ENAR) "Our Future as History"	O:01
	Jiqian Fang (National Group China Secretary) "Outcome Measurement for TCM and Challenge to Statistics"	O:02
	H. Sridhara (Indian Region President) "Sixty Years of IBS(IR) and Future of Biometry in India"	O:03
	Taerim Lee (Korean Region President) "Web Based Biostatistics Education Hub for East Asian Region"	O:04
	Toshiro Tango (Japanese Region President) " Major Activities of Biometric Society of Japan and Japanese Biostatisticians: Past, Present and Future"	O:05

Invited Session: Clinical Trials

Chair. *Shigeyuki Matsui* (Kyoto University School of Public Health, Japan)

Sunday,9th 11:00-12:30	*Yuantao Hao* (Sun Yat-sen University, China), *Jiqian Fang, Xinyuan Song* "Non-linear Factor Analysis Model and its Application to Evaluating the Equivalence of Questionnaires"	I:01
	Satoshi Morita (Kyoto University Hospital, Japan) "Determining the Effective Sample Size of a Parametric Prior"	I:02
	Masako Nishikawa (National Institute of Public Health, Japan), *Toshiro Tango* , *Megu Ohtaki* " Simple Statistical Tests for New Composite Hypotheses in Randomized Clinical Trial Reflecting the Relative Clinical Importance"	I:03

Contributed Session: Epidemiology

Chair: *Yutaka Matsuyama* (University of Tokyo, Japan)

Sunday,9th 14:00-15:30	*Ya Fang* (University of Xiamen, China) "Probability Prediction in Multistate Survival Models for Patients with Chronic Myeloid Leukaemia"	C:01
	Sachiko Tanaka (Tokyo University of Science, Japan) "Inverse Probability Weighted Estimators in the Stratified Nested Case-Control Sampling Methods"	C:02
	Koji Yonemoto (Kyushu University, Japan), *Atsushi Kawaguchi, Yumihiro Tanizaki, Yutaka Kiyohara, Takashi Yanagawa, Young K. Truong* "Application of Functional ANOVA Models for Hazard Regression to the Hisayama Data"	C:03
	Shizue Izumi (Oita University, Japan), *Yoshinori Fujii* "Estimating the Power of the Likelihood Ratio Test in the Cohort-Based Nested Case-Control Studies"	C:04

Contributed Session: Bioinformatics

Chair: *Seiya Imoto* (University of Tokyo, Japan)

Sunday,9th 16:00-17:30	*Tomonori Oura* (Kyoto University School of Public Health, Japan), *Shigeyuki Matsui, Koji Kawakami* "Sample Size Calculations Based on Exact Distribution of False Discovery Proportion in Microarray Experiments"	C:05
	Akihiro Hirakawa (Pharmaceuticals and Medical Devices Agency, Japan), *Yasunori Sato, Chikuma Hamada, Isao Yoshimura* "A Test Statistic Based on Shrunken Sample Variance for Identifying Differentially Expressed Genes in Microarray Data Analysis"	C:06
	Yoichi M. Ito (University of Tokyo, Japan), *Yasuo Ohashi* "Measurement Scale Categorization and Its Resolution. A Gene Reduction Approach to the Microarray Data Analysis"	C:07
	Takeharu Yamanaka (National Kyushu Cancer Center, Japan), *Shigeyuki Matsui* "Survival Prediction Using Top Ranking Significant Genes in Cancer Prognostic Studies with Microarrays"	C:08
	Mira Park (Eulji University, Korea), *Yoo-Jin Jang, Myung-Hoe Huh* "Applications of Minimal Spanning Tree and Self-Organizing Map in Microarray Data Analysis"	C:09

Invited Session: Bioinformatics

Chair: *Masaaki Matsuura* (Japanese Foundation for Cancer Research, Japan)

Monday,10th 9:00-10:30	*Jae Won Lee* (Korea University, Korea), *JungBok Lee, Shin-Jae Lee* " Statistical Tools for Protein Identification Based on Mass Spectrometry Data: A review"	I:04
	Seiya Imoto (University of Tokyo, Japan) "Bioinformatics Approach Towards Drug Target Gene Discovery"	I:05
	Masaru Ushijima (Japanese Foundation for Cancer Research) "Analyses of OMICS Data in Medical Informatics"	I:06

Keynote Lecture

Chair: *Thomas Louis* (Johns Hopkins Bloomberg School of Public Health, USA)

Monday,10th 11:00-12:00	*Toshiro Tango* (National Institute of Public Health, Japan) "Tests for Spatial Randomness: Detection of Disease Clustering and Outbreak Threat"	K:01

Invited Session: Epidemiology

Chair: *Tosiya Sato* (Kyoto University School of Public Health, Japan)

Monday,10th 13:30-15:00	*Ayanendranath Basu* (Indian Statistical Institute, India), *Sumit Gupta, Wen-tao Huang* " Tests of Hypothesis about the Kappa Statistic based on the Goodness-of-fit Approach"	I:07
	Satoshi Hattori (Kurume University, Japan), *Takashi Yanagawa* "Mantel-Haenszel Estimators for Irregular Sparse K 2 X J Tables"	I:08
	Kunihiko Takahashi (National Institute of Public Health, Japan), *Toshiro Tango* "Scan Statistics for Disease Clustering"	I:09

Contributed Session: Clinical Trials 1

Chair: *Satoshi Morita* (Kyoto University Hospital, Japan)

Monday,10th 15:30-17:00	*Shiro Tanaka* (University of Tokyo, Japan), *Yutaka Matsuyama, Yasuo Ohashi* " Estimating Surrogate Endpoints Defined by Principal Causal Effects"	C:10
	Anthony Hayter (University of Denver, USA), *Chen-ju Lin* "Recent Advances in Stepdown Procedures for Identifying Inferiority Among Treatments in Clinical Trials"	C:11
	Takahiro Hasegawa (SHIONOGI & CO., LTD., Japan), *Toshiro Tango* "Permutation Test Following Covariate-Adaptive Randomization in Randomized Controlled Trials"	C:12
	Tetsuhisa Miwa (National Institute for Agro-Environmental Sciences, Japan) "Comparisons Between Three Treatments Including a Placebo and a Control by the Multiple Confidence Procedure"	C:13

Contributed Session: Biostatistics in General

Chair: *Shizue Izumi* (Oita University, Japan)

Tuesday,11th 9:00-10:30	*Lilia L. Ramirez-Ramirez* (University of Waterloo, Canada), *Mary E. Thompson* "Statistical Inference for Outbreaks in a Population with a Contact Network Structure"	C:14
	Takashi Omori (Kyoto University School of Public Health, Japan), *Takashi Sozu, Isao Yoshimura* " Several Challenges by Biostatisticians for Developing a New Animal Test Method"	C:15
	Hyonggin An (Korea University, Korea) "Bayesian Analysis of Repeated Data with Many Zeros: Application to the Longitudinal Adolescent Substance Abuse Study"	C:16
	Tetsushi Komori (Bayer Yakuhin, Ltd., Japan), *Takashi Ohmori, Tosiya Sato* " Consistency of Signal Measures with Epidemiologic Effect Measures"	C:17

Contributed Session: Clinical Trails 2

Chair: *Osamu Komiyama* (Pfizer Japan Inc., Japan)

Tuesday,11th 11:00-12:30	*KyungMann Kim* (University of Wisconsin-Madison, USA) "An Independent Statistical Center in Support of the Data and Safety Monitoring Board: The Adenoma Prevention with Celecoxib (APC) Trial"	C:18
	JungBok Lee (Korea University, Korea)*,Byoung Cheol Jung,Hong Euy Lim,Chol Shin* "An Improved Estimating Method of QT interval for Adjusting Heart Rate: A Multivariate Approach"	C:19
	Masayuki Henmi (Institute of Statistical Mathematics, Japan)*, John B. Copas, Shinto Eguchi* " A Sensitivity Analysis Allowing for All Possible Selection Processes of Studies in Meta Analysis"	C:20
	Hiroyuki Uesaka (Eli Lilly Japan, Japan) "Sample Size Allocation to Regions in a Multiregional Trial"	C:21

Poster Session

9-10th 9:00-17:00	*Satoshi Teramukai* (Kyoto University Hospital, Japan), *Satoshi Morita* "Bayesian Predictive Multi-Stage Design for Phase II Single-Arm Clinical Trials: A Case Study"	P:01
	Hyo-Il Park (Chong-ju University, Korea), *Soo-Duck Lim, Joong-Jae Cho* "Hypothesis Test Under the Additive Hazards Model"	P:02
	Masahiko Gosho (Kowa Co. Ltd., Japan), *Chikuma Hamada, Isao Yoshimura* " Study on the Criterion for Selecting the Working Correlation Structure in Generalized Estimating Equation"	P:03
	Yumiko Uematsu (Tokyo University of Science, Japan), *Chikuma Hamada, Isao Yoshimura* "Statistical Method for Evaluating the Efficacy of a Drug for Osteoporosis on the Occurrence of Bone Fractures as the Primary Endpoint"	P:04
	Masayuki Yamada (Tokyo University of Science, Japan), *Chikuma Hamada, Isao Yoshimura* "Study on the Effect of Random Effects Included in the Analysis Model for In Vitro Pharmacological Data Adaptable to Four Parameter Logistic Model"	P:05
	Tetsuji Tonda (Hiroshima University, Japan), *Kenichi Satoh, Hiromi Kawasaki, Takeshi Shimamoto, Teruyuki Nakayama, Kota Katanoda, Tomotaka Sobue, Yasuto Sato, Naohito Yamaguchi, Megu Ohtaki* " Statistical Analysis of Spatial-Time Heterogeneity of Cancer Mortality Risk Based on Growth Curve Model"	P:06
	Kenichi Satoh (Hiroshima University, Japan), *Hirokazu Yanagihara* "Modified Cp in Multivariate Ridge Regression"	P:07
	Keiichi Sugino (Mitsubishi Tanabe Pharma Corporation, Japan), *Yasuo Ohashi, Qian Gong* "Multinational Clinical Trials in East Asia"	P:08
	Keiko Otani (Hiroshima University, Japan), *Megu Ohtaki, Keiko Hiyama, Kenichi Satoh, Eiso Hiyama* "Two Dimensional Summarization for Affymetrix GeneChip Probe Level Data Based on Functional States of Gene-ON/OFF"	P:09
	Kazue Yamaoka (National Institute of Public Health, Japan), *Toshiro Tango* "Effects of Lifestyle Modification on Metabolic Syndrome: Resolution Rate and Combining Multiple Endpoints in Meta-Analysis"	P:10
	Mihoko Minami (Institute of Statistical Mathematics, Japan) "A New Feature Extraction Method from very Non-Normal Data: Analysis of Multivariate Catch and Bycatch Data by Purse-Seine Tuna Fisheries"	P:11
	Yukikazu Hayashi (Tokyo University of Science, Japan), *Chikuma Hamada, Isao Yoshimura* " Statistical Pharmacokinetic Modeling of Controlled-Release Analgesics combining Immediate-Release and Sustained-Release Components to design an appropriate Drug Delivery"	P:12

Domestic Meeting

Tuesday, 11th 13:30-17:00	Biometric Seminar: Global Clinical Trials (Sponsored by Japanese Biometric Society)

Abstracts

K:01

Tests for Spatial Randomness:

Detection of Disease Clustering and Outbreak Threat

Toshiro Tango[1]

[1]Department of Technology Assessment and Biostatistics, National Institute of Public Health, Saitama, Japan

In epidemiological studies, it is often of interest to evaluate whether a disease is randomly distributed over time and/or space after adjusted for a known heterogeneity, which may provide clues to the etiology of disease. To do this, we can apply tests for spatial randomness, or disease clustering. On the other hand, in the aftermath of the World Trade Center attacks in September 11, 2001 and the anthrax-laden letters that followed in October 2001, a syndromic surveillance has been poised for deployment across USA. As a major analytical method for outbreak detection, a software SaTScan of Kulldorff's spatial scan statistic, a test for disease clustering, has been implemented in several syndromic surveillance systems.

In this talk, first, I review existing tests for disease clustering and focus on two specificc tests for some reason: one is called an index for disease clustering and the other is a scan statistic. Roles, advantages and disadvantages of these test statistics are discussed. These tests are illustrated and compared with several real temporal and spatial data. Second, I go on to describe the recent development of scan statistics associated with timely detection of outbreak threat in syndromic surveillance.

O:01

Our Future as History

Thomas A. Louis[1]

[1]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health

These are exciting and challenging times for the IBS and professional societies in general. The challenges require that we actively plan for our future and consider "Our Future as History" because that which lies ahead becomes the present and the present becomes our history. To plan for the future, I build on themes identified in my presidential address in Montreal, outlining our current status and initiatives, predicting and highlighting implications that call for expansions of our current activities and creation of new ones. These will ensure that we create our desired future and thereby produce a proud legacy.

O:02

Outcome Measurement for TCM and Challenge to Statistics

Jiqian Fang[1],Fengbin Liu [2]

[1]Research Center of Health Information; Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University [2]The Teaching Hospital, Guangzhou University of Traditional Chinese Medicine

Initially according to the philosophy of traditional Chinese medicine (TCM), the clinical effects of TCM were evaluated bythe improvement on "ZHENGS". This sounds reasonable to TCM, but lacks common language with the modern western medicine. The "objective indexes" especially the laboratory tests have had been adopted in evaluation of clinical effects by "modern"TCM although there were no any relationship between the philosophy of TCM and these indexes and tests. This is really unfair to TCM and makes some "modern" TCM people being mixed, even no longer be subject to TCM seems to me. Good news is that QOL and PRO could be a common platform for both of modern western medicine and TCM to work together andcompete with each other. In fact, QOL and PRO have had been much familiar by TCM people for thousands years as part of their tradition, only but the measurement of QOL and PRO having not been so systematic as those done today in modern western medicine. Now some of the TCM people have been aware with this and start to develop scientific-based instruments to measure QOL and PRO with the integration of rich experience of TCM and modern western medicine. It could be foreseen that the two systems of medicine, TCM and modern western medicine, may continue to progress on their own track, shake handand communicate on the common platform of QOL and PRO, for the same target of serving the patients.However, the statistical methodology for the analyses of questionnaires on QOL and PRO is far from mature today. There arefull of challenges to Statistics and Biostatistics. The researchers regard the measures for the item taking "value" within finite options as a continuous variable or a discrete variable with equal-distance integers, rather than an ordinal variable; And then a package of item response theory, factor analysis and structure equation model etc. becomes a routine in data analysis. This is a big mistake but the non-statisticians have no way to get rid of. If you do regard the response to such items as ordinal variables, how can you work out a series of multivariate analysis for the data of questionnaires as those for continuous variables? how can you work out analysis for longitudinal observations by questionnaires? In one word, the platform of QOL and PRO are also an arena for statisticians and bio-statisticians to play on. Do not miss it.

O:03

Sixty Years of IBS(IR) and Future of Biometry in India

H.Sridhara [1]

[1]Biostatistics & Bioinformatics, Thrombosis Research Institute, India

The Biometric Society in India was established in 1947, simultaneously with the other four regions viz. US, Briton, France and Australia. IBS(IR) is celebrating the Diamond Jubilee this year. This talk traces the history of growth and development of Biometry in India in general and the contributions of Indian biometricians to the subject in particular. The implications of globalization on research and development of biometry and the issues concerning that in coming years are also discussed.

O:04

Web Based Biostatistics Education Hub for East Asian Region

Taerim Lee[1]

[1]Department of Information & Statistics, Korea National Open University, Korea

e-Learning is an on-line education defined as the self paced or real time delivery of training and education over the internet to an end user device. In view of biostatistical education e-Learning has many advantages such as reduction of education cost, repeated learning, customized education, and self-paced learning.

e-ABEH system for Biostatistics, Bioinformatics and Medical Informatics Education has improved the lack of two-way communication and repetition, the main weakness of the existing face to face class and written text. And it has extended the opportunity of learner by operating a variety of individual curriculum on the basis of e-learning.e-ABEH is an web based network under Far East Asian Biometric Region consortium we call ABEH(Asian Biometric Education Hub) for promoting cooperation among Far East Asian Biometric Region in regard to Biostatistics, Bioinformatics , Medical Informatics and statistical consulting.

The aim of e-ABEH is to first initiate online research network that allows Far East Asian Biometric University partners to continuously exchange Biostatistics, Bioinformatics and Medical Informatics related academic and practical experiences.

Secondly it is to use the online research network for conducting collaborative research projects and practical biostatistical consulting among the ABEH members. With these aims, three sub-research themes and seven working group activity to be performed on the e-ABEH network.

This paper describes the e-learning community e-ABEH for Biostatistical education that anyone who wants to study could study anywhere, anytime with web and multimedia system under the Asian member regions consortium. Those e-learning contents will be constructed with the components e-lecture, e-book, simulation experiment, web link for reference, computer-aided tutor for statistical learning, self-evaluation system, and a statistical package for the practice of data analysis and biostatistical consulting center.

O:05

Major Activities of Biometric Society of Japan and Japanese Biostatisticians:Past, Present and Future.

Toshiro Tango[1]

[1]Department of Technology Assessment and Biostatistics, National Institute of Public Health, Saitama, Japan

At the end of 2005 Biometric Society of Japan (BSJ) cerebrated a quarter of a century of its establishment, a 25-year period over which the number of BSJ members has increased to about 450 from 220 and it has engaged a wide range of research and education. In this talk, I shall review the major activities of BSJ and the achievements that BSJ members have made by investigating the temporal trend of published papers in such journals as Japanese Journal of Biometrics, Biometrics and Statistics in Medicine. I will further investigate the Japanese achievements published in the Encyclopedia of Statistical Sciences and the Cambridge Dictionary of Statistics. Based on these investigations, I would like to discuss the conditions that, I think, could improve the present situation and infuence the future activities and status of Japanese Biostatisticians.

I:01

Non-linear Factor Analysis Model and its Application to Evaluating the Equivalence of Questionnaires

Yuantao Hao[1],Jiqian Fang[1],Xinyuan Song[2],Mick Power[3]

[1]Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, China [2]Department of Statistics, Hongkong Chinese University [3]Department of Clinical Psychiatry, University of Edinburgh, Edinburgh, UK

The increasing international collaboration in health-related quality of life research has created a need for cross-culturally valid instruments for outcome assessment. According to the definition, Equivalence concerns if there exists the same factor structure and factor loading matrix among different language/culture versions of questionnaire from the aspect of factor analysis. Accordingly, multi-group confirmatory factor analysis can be used to assess equivalence of questionnaires. In the traditional confirmatory factor analysis, a set of observed variables is expressed as a linear combination of a number of latent variables and a residual vector. There is a strong demand to extend linear model to non-linear model since non-linear relationship such as the interaction of latent variables exists in many research fields. The difficulties of non-linear factor analysis are how to establish the non-linear model and how to estimate parameters. Methods used by now have some deficiencies and difficulties. In this study, the author established a generic non-linear factor analysis model, put forward parameters estimation methods, and extended the one-sample non-linear model to multi-sample non-linear model. At first, the author formulated a generic non-linear factor analysis model, and then parameters were estimated by using maximization likelihood method. Owing to the non-linear relationship of latent variables, the multiple integral of the log-likelihood function based on the observed data does not have an explicit form. Hence, it is difficult to obtain the estimates by maximization of the log-likelihood function directly. Data augmentation method was considered to solve this problem. The observed data was augmented with the matrix of latent variables which was treated as a hypothetical missing data. Then the ML estimates were obtained by EM algorithm. We used Louis function and random sample generated in the MH algorithm to obtain standard error estimates. BIC criterion was used on model selection in multi-group non-linear factor analysis. Results of simulation study illustrated that the estimates were closed to their true values, and model selection results were approximately the same as the real situation. It is implied that the proposed method performed well. In addition, a real example is reported.

I:02

Determining the Effective Sample Size of a Parametric Prior

Satoshi Morita[1]

[1]Department of Clinical Trial Design and Management, Translational Research Center, Kyoto University Hospital, Kyoto, Japan

We present a definition for the effective sample size of a parametric prior distribution in a Bayesian model, and propose methods for computing the effective sample size in a variety of settings. Our approach first constructs a prior chosen to be vague in a suitable sense, and updates this prior to obtain a sequence of posteriors corresponding to each of a range of sample sizes. We then compute a distance between each posterior and the parametric prior, defined in terms of the curvature of the logarithm of each distribution, and the posterior minimizing the distance defines the effective sample size of the prior. For cases where the distance cannot be computed analytically, we provide a numerical approximation based on Monte Carlo simulation. We provide general guidelines for application, illustrate the method in several standard cases where the answer seems obvious, and then apply it to some non-standard settings.

I:03

Simple Statistical Tests for New Composite Hypotheses in Randomized Clinical Trial Reflecting the Relative Clinical Importance

Masako Nishikawa[1],Toshiro Tango[1],Megu Ohtaki[2]

[1]Department of Technology Assessment and Biostatistics, National Institute of Public Health, Japan
[2]Department of Environmetrics and Biometrics, Research Institute for Radiation Biology and Medicine, Hiroshima University, Japan

In confirmatory clinical trials, it is recommended that the most important endpoint (EP) should be chosen as primary. However, it is often difficult to choose only one primary EP in some therapeutic area. Such a trial set up multiple EPs which arise multiplicity problem in general. To avoid the multiplicity problem a combined EP can be considered. O'Brien (1984) proposed an ordinary least squares and a generalized least squares approach for continuous variables under the assumption that the effects are equal across EPs. Pocock et al. (1987) extended the method to combine different types of variables into a single EP which is asymptotically normally distributed, and they suggested a formulation for unequal priorities to various EPs, however, there are no methods to measure the relative clinical importance quantitatively. We propose a new set of composite hypotheses taking the relative clinical importance between EPs into account for continuous variables. This formulation leads to a new test statistic, which can measure the relative clinical importance between EPs quantitatively and will be sensitive for such an alternative hypothesis that the effect for the more important EP of the new treatment is greater than that of the other EP even if the new treatment is superior to the control in both EPs. The size of the proposed test is explored by simulation. Our test is illustrated by an example. References O`Breien. (1984) Procedures for comparing samples with multiple endpoints. Biometrics 40, 1079 -1087.Pocock SJ., Geller NL. and Tsiatis AA. (1987) The analysis of multiple endpoints in clinical trials. Biometrics 43, 487-498.Keywords COMPOSITE ENDPOINT, ONE-SIDED TESTS, MULTIPLE ENDPOINTS

I:04

Statistical Tools for Protein Identification Based on Mass Spectrometry Data:A Review

Jae Won Lee[1],JungBok Lee[2],Shin-Jae Lee[1,3]

[1]Department of Statistics, Korea University, Seoul, Korea [2]Institute of Human Genomic Study, College of Medicine, Korea University [3]Department of Orthodontics, College of Dentistry, Seoul National University

Peptide Mass Fingerprinting (PMF) through mass spectrometry is a technique used to identify proteins by matching their constituent fragment masses (peptide masses) to the theoretical peptide masses generated from a protein or DNA database and widely applied in proteome research. To identify the protein from the high throughput mass spectrometric data, the database searching has emerged as a key platform in this field and several DB searching algorithms have been developed. Some researchers commented several factors influencing the quality of a mass spectrometry experiment. Missed cleavages, post-translational modifications of peptides and contaminants are important factors affecting the results of the mass spectrometric data analysis, but these factors have an influence on the identification process rather than the quality of the MS spectra. In this talk, we will review statistical algorithms for protein identification and evaluate the identification performance of current DB searching algorithms by simulation study. Our simulation result will provide the proteome researchers the insight for selecting the DB searching algorithm appropriate for their data.

I:05

Bioinformatics Approach Towards Drug Target Gene Discovery

Seiya Imoto[1]

[1]Institute of Medical Science, University of Tokyo, Tokyo, Japan

Microarray technology has produced a large volume of genome-wide gene expression profile data under various experimental conditions such as gene disruptions, gene overexpressions, shocks, cancer cells, etc. Along with this new data production, there have been considerable attempts to infer gene networks from such gene expression profile data and several computational methods have been proposed together with gene network models such as Boolean networks, differential equation models and Bayesian networks. While the paradigm of using microarray technology with the clustering technique has made tremendous impacts on biomedical research and practice, the strategy enhanced with computational gene network analysis has not yet been well examined for practical applications. In this talk, we show a computational method for identifying and validating drug target genes from DNA microarray gene expression data. To demonstrate the whole process of the proposed method, we analyze expression data from human endothelial cells. We generate new time-course data that reveal the responses of human endothelial cell transcripts to treatment with the anti-hyperlipidaemia drug fenofibrate. We also generate new data from 270 gene knock-down experiments in human endothelial cells. The fenofibrate-related gene network is estimated based on fenofibrate time-course data and 270 gene knock-down expression data by the proposed method. The estimated gene network reveals gene regulatory relationships related to PPARa, which is known to be activated by fenofibrate. Our gene networks have the potential to predict the mode-of-action of a chemical compound, discover more effective drug target and predict side-effects. Finally, the proposed computational analysis suggests that our strategy based on gene knock-down and drug-dosed time-course microarrays will give a new way to druggable gene discovery.

I:06

Analyses of OMICS Data in Medical Informatics

Masaru Ushijima[1]

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Bioinformatics is the science of using computers, databases, and math to organize and analyze large amounts of biological, medical, and health information by NCI definition. Major research area in the field of classical bioinformatics includes sequence analysis, protein structure prediction and comparative genomics. In the 'omics' era of cancer research, high-throughput analyses of 'omics' data such as genome, transcriptome and proteome data will have a great impact on diagnosis, prognosis, and therapy of cancer. In this presentation, we focus on medical informatics for personalized medicine and review recent methodologies for high-throughput analyses for genome-wide association study using SNPs, gene expression profile analysis and mass spectrometry data. In genome analysis, we introduce a method of association study using SNPs and haplotypes. Haplotype block structure is identified using an ancestor-derived model and the MDL principle. We show some examples that the appropriate haplotype block partitioning leads to increase the power of tests in association study. In transcriptome analysis, we breifly introduce a method of gene selection for the prediction of phenotypes using microarray datasets. Finally we introduce our new common peak approach, using mass spectrometry datasets for predicting effects on anticancer drugs. The original common peak method proposed by Fushiki et al. (2006) is a simple way to select the sensible peaks that are shared with many subjects among all detected peaks by combining a standard spectrum alignment and kernel density estimates. The key idea of our proposed method is to apply the common peak approach to each class label separately. Hence, the proposed method gains more informative peaks for predicting class labels, while minor peaks associated with specific subjects are deleted correctly. We used a SELDI-TOF MS data set from laser microdissected cancer tissues for predicting the treatment effects of neoadjuvant therapy using an anticancer drug on breast cancer patients. The AdaBoost algorithm is adopted for pattern recognition, based on the set of candidate peaks selected by the proposed method. The analysis gives good performance in the sense of test errors for classifying the class labels for a given feature vector of selected peak values.

I:07

Tests of Hypothesis about the Kappa Statistic based on the Goodness-of-fit Approach

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We consider the goodness of fit approach for performing tests of significance about the kappa statistic. The approach was suggested by Donner and Eliasziw (1992; Statistics in Medicine, 11, 1511-1519) who framed the parametric hypothesis testing problem about the kappa statistic (leading to other associated small sample inference) as a multinomial goodness-of-fit testing problem, for which they proposed the Pearson's chi-square statistic. Basu and Basu (1995; Statistics in Medicine,14,347-356) considered the use of some other members of the Power divergence family of Cressie and Read (1984; J. Roy. Statist. Soc. B, 46, 440-464) for this goodness of fit testing. However, when a specific alternative is of interest, all the standard goodness of fit tests can be quite poor in comparison with the most powerful test within the above family; in addition the asymptotic chi-square approximation for these statistics may be quite inadequate for small samples. Here we consider the results of a general investigation based on exact power computations which helps us to search for the most powerful test for each sample size given the appropriate parameters and identifies the randomized exact critical values. The advantages of this method are demonstrated with power and sample size comparisons.

I:08

Mantel-Haenszel Estimators for Irregular Sparse K 2 X J(J&gt2) Tables

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The Mantel-Haenszel estimator has a shortcoming that it cannot be calculated for certain sparse tables, called irregular, although it is consistent under sparse-data limiting model. In this paper, we propose a Mantel-Haenszel-type estimation procedure for such sparse K 2 X J tables when J&gt2, employing the idea of the projection-method by Yanagawa and Fujii (1995 JASA). The projection method projects log-transformed Mantel-Haenszel estimators for all K 2 X 2 subtables, called naive Mantel-Haenszel estimators, onto a linear space of log odds ratios. However, for sparse tables, all the naive Mantel-Haenszel estimators may not be calculated. We introduce alternative naive Mantel-Haenszel estimators using a graph representing K 2 X J tables and propose to apply the projection-method for these alternatives. In this way, we have infinitely many reasonable projection-method estimators. We propose a method to choose the optimal one among them by solving a quadratic optimization problem induced by the graph, where some graph-theoretic arguments play important roles to simplify the optimization problem. An illustration is provided with data from a case-control study. A simulation study is conducted, which indicates that the Mantel-Haenszel estimators are more stable than the estimators by the conditional logistic regression for sparse K 2 X J(J&gt2) tables.

I:09

Scan Statistics for Disease Clustering

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The circular spatial scan statistic proposed by Kulldorff (1995, 1997) has been widely used along with SaTScan software in epidemiological studies for cluster detection. To detect arbitrarily shaped clusters which cannot be detected by the circular scan statistic, some spatial scan statistics such as those developed by Duczmal and Assuncao (2004) and Patil and Taillie (2004) have proposed. Also Tango and Takahashi (2005) proposed a flexible spatial scan statistic along with FleXScan software. On the other hand, early detection of disease outbreaks enables public health officials to implement disease control and prevention measures at the earliest possible time. A time periodic geographical disease surveillance system based on a cylindrical space-time scan statistic proposed by Kulldorff (2001) has been used for disease surveillance. Recently, Takahashi et al have proposed a flexibly shaped space-time scan statistic for early detection of disease outbreaks based on the flexible spatial scan statistic.

All of these scan statistics are based on maximizing the likelihood ratio statistic. However, Tango and Takahashi (2005) showed an example that Duczmal and Assuncao's procedure detected quite large and peculiar shaped clusters that had the largest likelihood ratio, which caste a doubt on the validity of the model selection based on maximizing the likelihood ratio. Furthermore, Tango and Takahashi (2005) have indicated that the circular scan statistic tend to detect an unrealistically larger cluster than expected by absorbing surrounding regions where there is no elevated risk. One of reasons for detecting undesirable clusters is that the likelihood ratio statistic is derived only from the observed number of cases within the window Z, and the expected number within Z under the null hypothesis of no clustering. And the statistic ignores the variability of individual regions' risks included in Z.

We propose several scan statistics that can take such variability into account. Some data in Japan are used to illustrate the proposed scan statistics for purely spatial and space-time clustering. Power comparisons are also presented. These proposed scan statistics have better ability of pinpointing the assumed hot-spot cluster compared with the likelihood ratio statistic.

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C:01

Probability Prediction in Multistate Survival Models for Patients with Chronic Myeloid Leukaemia

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[Objective] Multistate survival experiments include various terminal events and competing-risk events. How to predict the probabilities with multistate survival models is of interest. The purpose of this study is to find an appropriate model suitable for a multistate survival experiment. [Methods] 634 patients with risk score 0 or 1 as an example were selected to illustrate the method of analysis from 3142 CML patients who underwent bone marrow transplantation between 1989 and 1997. The statistical methods which were used were log-rank test, Kaplan-Meier method, survival analyse and competing-risk method. [Results] After transplantation, there are four possible situations for a patient-- disease free, relapse but still alive, death before relapse, and death after relapse. The last three events are considered as treatment failure. First, we deal with the two events, relapse either death or not and death before relapse, as competing-risk causes which are the endpoints with transplantation as the starting point. The risk of death before relapse is higher than that of the relapse, especially in the first year after transplantation. Subsequently we analyse the effect of relapse time on the event of death after relapse which is the endpoint with relapse as the starting point by the Kaplan-Meier method. The result of patients with relapse time less than 12 months was much poor. Finally, the multistate survival models are developed which are detailed and informative based on the analysis of competing risks and Kaplan-Meier analysis. We make a further analysis on conditional probability with the multistate survival models for patients who are disease free and still alive at month 12 after transplantation. [Conclusions] It is possible for an individual patient to predict the four possible probabilities at any time, namely disease free, relapse but still alive, death before relapse, and death after relapse. Also the prognoses for relapse either death or not and death either before or after relapse may be given. Furthermore, the conditional probabilities for patients who are disease free and still alive in a given time after transplantation can be predicted.

C:02

Inverse Probability Weighted Estimators in the Stratified Nested Case-control Sampling Methods

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Stratified nested case-control designs are widely used in the expectation that these methods may increase precision relative to simple nested case-control design. Although conditional logistic regression is used for analysis of data with matching, it will be inefficient because it does not use all subjects at risk. In this talk, we introduce the simple- and augmented- inverse probability weighted (IPW) estimator of Cox regression parameter under stratified sampling designs. We estimate selection probability and conditional expectation of missing covariate using nonparametric methods that incorporates information of matching factors. The performance of the proposed method is investigated through simulation studies. From the results of simulation studies, our proposed methods improved showed superior efficiency to the conditional logistic model.

C:03

Application of Functional ANOVA Models for Hazard Regression to the Hisayama Data

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A methodology for modeling covariate effects on the time-to-event data is developed. The covariates are allowed to be time-dependent and their effects are modeled using polynomial splines in order to account for possibly non-linear effects. The methodology is applied to examine the effects on the incidence brain infarction based on a cohort study in Hisayama, Japan. The results indicate that at least two non-linear effects are significant (body mass index and systolic blood pressure) and there is a time-varying drug effect. The resulting significant risk factors are assessed by the proposed method which is more flexible and hence less biased than the traditional procedures where linear effects are imposed. These results are extremely important to the local medical investigation. In particular, more insight has been gained by examining the non-linear effects.

C:04

Estimating the Power of the Likelihood Ratio Test in the Cohort-based Nested Case-control Studies

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Cohort-based molecular epidemiologic studies have been conducted actively to ascertain the disease mechanism with candidate biologic markers using the stored biological samples accumulated over years. It is important to thoroughly consider what design is the best under the given study conditions. Possible choices include a case-cohort design, a simple case-control design, a nested case-control design, and a case only design. Some designs have pro and cons to others. A nested case-control design is relatively efficient in estimating the effects of the target variable. Therefore, we propose a new method to estimate the power of the likelihood ratio test in the cohort-based nested case-control studies.

In our settings of the power calculation, the cohort data are assumed to include the complete information on the event status of the disease, the observed time, and the exposure. Frequently the information of the confounder is missing in the cohort data so that the marginal distribution of the confounder is obtained from other studies to randomly assign the value to the individuals of the cohort. Using such interpolated cohort data, the effects of the exposure and the confounder can be estimated with the proportional hazard model. For the cohort-based nested case-control data, the controls are sampled from the risk set defined for each event time. In our method, a surrogate case is additionally sampled from the risk set using the likelihood-based sampling weights as a replacement of the original case. Likelihood ratio test is used at the level of 0.05 to examine a null hypothesis in that the parameter estimate is zero. The power is computed as a probability of rejecting a null hypothesis when the alternative hypothesis is true. Our method may be fragile to the distortion of proportional hazard assumption.

The simulation studies were conducted to examine the feasibility of our method. The event status and the observed time in the cohort data were defined with the Weibull distribution and the exponential distribution. Five hundred nested case-control data were created to each 500 cohort data. All computations were done with R software. As results, the mean power of our method was close to the power of the classic method and the R programming for the simulation studies was fairly straightforward. As a conclusion, our proposed method is feasible and useful to estimate the power of the likelihood ratio test in the cohort-based nested case-control studies.

C:05

Sample Size Calculations Based on Exact Distribution of False Discovery Proportion in Microarray Experiments

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Microarray gene expression analysis is one of the standard tools for screening for differentially expressed genes among different diagnostic or prognostic classes of disease. In order to detect differential genes, thousands of univariate tests are usually conducted simultaneously, with control of the false discovery rate (FDR), which is defined as the expectation of the false discovery proportion (FDP), the number of false positive genes out of the number of genes declared positive.

To obtain a reliable list of differential genes, more attention should be paid to experimental design, including determination of the number of samples. Many methods for sample size calculations recently developed are based on marginal FDR (mFDR), which is the ratio of the expectation of the numerator to that of the denominator of FDP, as an approximation of FDR. However, this approximation can be inaccurate for correlation among genes by virtue of co-regulation, potentially resulting in a serious failure in determining sample sizes.

In this paper, we propose to use an exact distribution of FDP, which allows exact control of distributional characteristics of FDP, including the mean (i.e., FDR) and percentiles. Our methods can accommodate block-wise gene correlation structures with various correlation coefficients and various effect sizes on the phenotype variable. We demonstrate that our sample size calculations are accurate compared with previous sample size calculations [(1,2)], through Monte Carlo simulations and application to real datasets from clinical studies for multiple myeloma and lymphoma.

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C:06

A Test Statistic Based on Shrunken Sample Variance for Identifying Differentially Expressed Genes in Microarray Data Analysis

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Choosing an appropriate test statistic for comparing the gene expression levels under different conditions is essential for identifying differentially expressed genes. For identifying truly differentially expressed genes, it is necessary to suppress both false positives, which are genes that are falsely identified as differentially expressed genes, and false negatives, which are genes that are falsely not identified as differentially expressed genes. Both false positives and false negatives mainly arise due to the underestimation and overestimation of the variance of gene expression levels, respectively. The Welch t-statistic leaves both the underestimation and overestimation of variance uncontrolled, resulting in an increased risk of both false positives and false negatives. The t-type score proposed by Pan et al. (2003) with a correction term added to the denominator of the Welch t-statistic can suppress false positives by controlling the underestimation of variance, but it can not suppress the overestimation. To control the overestimation, we devised a variance stabilized t-type score by placing shrunken sample variances of the James-Stein type in the denominator of the t-type score. The shrunken sample variances, which can utilize information across genes according to the James-Stein shrinkage concept, can control the overestimation of variance. The variance stabilized t-type score, therefore, can suppress both false positive and false negatives. We conducted a simulation study to compare the performances of the Welch t-statistic, t-type score, and variance stabilized t-type score, demonstrating that the variance stabilized t-type score was better than or at least as good as the t-type score. In particular, the variance stabilized t-type score outperformed the t-type score when the sample size was smaller than 5 in each group or the proportion of differentially expressed genes was smaller than 5%. As a result of application using Significance Analysis of Microarray (SAM) (Tusher et al., 2001) to colorectal cancer data (Provenzani et al., 2006), the variance stabilized t-type score might control the overestimation of variance.

C:07

Measurement Scale Categorization and its Resolution.

A Gene Reduction Approach to the Microarray Data Analysis.

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In the microarray data analysis, selection of the important gene must be needed because the sample size is usually limited in contrast to the huge number of genes. The measurement error of the microarray data is prone to be large, therefore the subtle difference of gene expression cannot be detected. In this study, we propose the measurement scale categorization according to both the measurement error and the categorization error. This approach is to break continuous gene expression measurement into some prespecified categories and by which the expression for a gene can be classified to one of a finite expression patterns. The simulation study revealed that the power loss associated with this approach was large when the effect size is small. However this property is useful for eliminating the genes which shows a small change. We applied this approach to a clinical data for primary breast cancer.

C:08

Survival Prediction using Top Ranking Significant Genes in Cancer Prognostic Studies with Microarrays

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Microarray technology promises a sound possibility for developing patient prognostic markers at molecular level. Primary analysis for such studies is to screen a subset of relevant, prognostic genes from (ten of) thousands of candidates and then is followed by an investigation regarding prognostic power of the screened subset as a supplemental analysis. However, many methods for survival prediction actually intend to use a whole full set of genes for prediction or to use gene subsets that are selected without regard to the primary analysis. Accordingly, no formal statistical comparison among predictors has not been conducted under the practical limitation of significant genes being chosen previously. Our study is thus concerned with assessing predictive accuracy of several predictors on the condition that we focus on a selective subset of relevant genes from the primary analysis. We evaluated several linear predictors including principal components[1], partial least squares[2], compound covariates[3], and ridge regressions[4]. The predictive performance of these methods were measured firstly by using simulated data under various conditions on the total number of top ranking genes, their correlation structures, and the degree of linkage to survival outcome. The reliability and validity of their predictive accuracy arising from cross-validation split of whole data into training and test sets were also evaluated. Then, we used publicly available microarray data from cancer clinical studies and examined the applicability of the results from simulated data to them. Integrating these investigations has revealed that there is large predictive heterogeneity among predictors and some of methods often fail to achieve enough performance.

We have also investigated a possible impact of the selection of top ranking genes. Primary identification of gene subsets is a crucial step in prognostic studies although most cases simply rely on ranking univariate Cox scores. We will report the impact of various summary statistics used for primary screening, including log hazard ratios and empirical Bayes estimators, on predictive performance of predictors.

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C:09

Applications of Minimal Spanning Tree and Self-organizing Map in Miroarray Data Analysis.

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Self-organizimg map (SOM) is an unsupervised learning neural network method and it is useful to present high-dimensional data to low dimensional map. However, there are several problems in applying SOM such as determination of the size and shape, ineffectiveness in visualization, and so on. Minimal spanning tree is a tree in which each taxon is connected by a line to its most similar neighbor. It can be used for pattern recognition of large dataset. In this study, we suggest a measure for determining proper size of the map using minimal spanning tree. And we also propose a method for partitioning and choosing the number of clusters. It is based on the distance between objects connected by MST on SOM. The methods are applied to some variants of SOM, such as subnode-SOM and PC-SOM. We also illustrate the proposed methods using two well-known microarray data sets: the leukemia data set(Golub et al., 1999) and the lymphoma dataset(Alizadeh et al.,2000).

C:10

Estimating Surrogate Endpoints Defined by Principal Causal Effects

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In clinical trials, comparison of treatments for the outcome of primary interest such as survival time may require a long follow-up before yielding useful results. Because of this, there is increasing interest in the use of surrogate endpoints to make decisions about treatment efficacy. Frangakis and Rubin (2002) proposed a principal surrogate, which was defined by potential values of surrogate endpoints. However, it is impossible to observe joint distribution of potential surrogate endpoints without untestable assumptions. In this talk, we propose an estimation method of the principal surrogate under monotonicity assumption, which states that there is no subject who would not have a response under test arm, but have a response under control arm. We also applied the proposed method to a clinical trial data of advanced prostate cancer.

C:11

Recent Advances in Stepdown Procedures for Identifying Inferiority among Treatments in Clinical Trials

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This talk considers the problem of identifying which treatments are not the best treatment in a one-way layout, which has many important applications in screening trials for new product development. In Hayter (2007) "A Combination Multiple Comparisons and Subset Selection Procedure to Identify Treatments Strictly Inferior to the Best," Journal of Statistical Planning and Inference, a procedure has been developed that selects a subset of the treatments containing only treatments that are known to be strictly worse than the best treatment or treatments. In addition, simultaneous confidence intervals are obtained which provide upper bounds on how worse each treatment can be compared with the best treatment. In this way the new procedure shares the characteristics of both subset selection procedures and multiple comparison procedures. Also, in Lin and Hayter (2007) "A Stepdown Procedure with Feedback for Identifying Inferiority among Three Treatments" a stepdown procedure is developed that uses feedback from the first stage to the second stage which improves its operating characteristics. The advantages accruing from this feedback are demonstrated.

C:12

Permutation Test Following Covariate-adaptive Randomization in Randomized Controlled Trials

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In randomized controlled trials, eligible and consenting patients are recruited and randomly allocated to treatments. Patients are never randomly sampled from large population of patients on treatments under study. Therefore, it is natural to apply permutation test under the *randomization model*, where it is assumed that the treatment assignments is random and that the set of observed responses is fixed under the null hypothesis. However, most of the statistical analyses are still based on the concept of *population model*, where patients are assumed to be randomly sampled from populations.

In this article, we examined the property of *permutation test* following Pocock-Simon's covariate-adaptive randomization using the difference in means as a test statistic under the randomization model in comparison with that of *t* test and analysis of covariance under the population model. Furthermore, we compared the size and average power of permutation test with that of *t* test and analysis of covariance via Monte Carlo simulation. When complete covariate balance is attained, permutation test is proved to be identical to the analysis of covariance. When there is a little covariate imbalance, the average power of permutation test is shown to be slightly lower than that of analysis of covariance. Unless the effects of covariate is negligible, *t* test is shown to be inadequate in that its size is quite lower than the nominal α level. Our results suggest that permutation test following Pocock-Simon's covariate-adaptive randomization can be used as a useful alternative to traditional population-based design in a confirmatory randomized controlled trial with important prognostic factors.

C:13

Comparisons between Three Treatments including a Placebo and a Control by the Multiple Confidence Procedure

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Takeuchi (1973) proposed a multiple confidence procedure for multiple decision problems in his book "*Studies in Some Aspects of Theoretical Foundations of Statistical Data Analysis*" (in Japanese).This procedure is based on a partition of the parameter space, and it is closely related to the recent development of the partitioning principle for multiple comparison procedures.

In our talk we apply the multiple confidence procedure to the problem of comparing three treatments: placebo, control and test treatments.Let μ_0, μ_C, μ_T be the population means of the placebo, control ant test treatments, respectively.Then the total parameter space is partitioned into four disjoint regions:

(1) $H_0^{(1)}$: $\mu_C + \Delta_U < \mu_T$ (superiority)
(2) $H_0^{(2)}$: $\mu_C - \Delta_L \leq \mu_T \leq \mu_C + \Delta_U$ (equivalence)
(3) $H_0^{(3)}$: $\mu_0 < \mu_T < \mu_C - \Delta_L$ (effectiveness against control)
(4) $H_0^{(4)}$: $\mu_T \leq \mu_0$ (futility)

We construct test procedures for the null hypotheses $H_0^{(i)}$.Then the possible decisions are obtained by collecting all the accepted null hypotheses.

C:14

Statistical Inference for Outbreaks in a Population with a Contact Network Structure.

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For diseases that spread in a population with the direct contact of its individuals, traditional epidemic models assume that every susceptible individual is homogeneously exposed to the agent. However it has been observed that for some diseases, the outbreaks do not evolve uniformly through populations making evident that some epidemics are heavily affected by the population connectivity patterns in which the infective agent spreads ([1], [2] and [3]).

Recent epidemic models incorporate the heterogeneous individual exposure based on a contact structure that is built in terms of random graphs [4]. Random graphs or networks have been widely used to model several systems, including the World Wide Web, metabolic and protein and language, and have been observed to model social relationships like the number of sexual partners [5],

Since the basic reproductive number (*)/ replacement number (**), together with the threshold theorem (***) are used to plan and evaluate the control measures for outbreaks, it is important to improve its estimation, separating it from the particular population contact network structure in which the data is observed. In this work we show the methodology for statistical estimation for outbreaks in a population with a network structure, and some examples.

Special emphasis is made in the Reed-Frost model that evolves in a contact network.

Footnote

(*) Average number of new infected individuals produced by a contact with one infected individual in a complete susceptible population.

(**) Average number of new infected individuals produced by a contact with one typical infected individual

(***) States the critical value of the basic reproductive number (replacement number) above which the probability that the outbreak develops into an epidemic is greater than zero.

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C:15

Several Challenges by Biostatisticians for Developing a New Animal Test Method

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To identify chemicals of skin sensitization potential is an aim in regulatory toxicology. The Local Lymph Node Assay (LLNA) is one of the test methods for the purpose, which has been developed and validated. Since the standard LLNA, however, requires the use of radioisotopes, the facility which conducts the experiments of the test method is limited. Then, the development of the alternatives for the standard LLNA is expected. A modified LLNA proposed by Daicel ltd. based on ATP content (LLNA-DA) is a candidate of alternatives for the standard LLNA (1).

For a new assay to be recognized as a test method, the validated data for intra- and inter-laboratory reproducibility and relevance is required (2). Since the LLNA-DA had no data for inter-laboratory reproducibility, two validation studies of the LLNA-DA were conducted in 2006-2007. Due to limited funding and a short time schedule for the project, there were many challenges involved in the studies: how to collect data from each experiment laboratory, how to allocate masked chemicals for laboratory experiments, how to measure the inter-laboratory reproducibility, how to evaluate transferability and so on. We prepared formatted data files in order to collect data correctly and a program for random allocation that considers the degree of skin sensitization. We also developed confidence intervals and inter-laboratory variance of an index for the judgment on skin sensitization potential, and proposed a measure for transferability.

Although these works are simple and may not be new ones for the statistical methodology, we believe that the works by biostatisticians enable researchers in the area not only to evaluate the pure inter-laboratory reproducibility avoiding other errors but also to show successfully high performances of the LLNA-DA.

We report these statistical challenges and results in the LLNA-DA validation studies.

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C:16

Bayesian Analysis of Repeated Data with ManyZeros: Application to the Longitudinal Adolescent Substance Abuse Study

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Data with too many zeros are quite common in the longitudinal substance abuse research. Standard statistical methods for those data such as repeated measures analysis of variance or generalized linear mixed model may produce invalid inferences. As appropriate alternatives to standard methods, Tooze et. al. (2002) proposed a two-part model with random effect for continuous outcomes while Hall (2000) proposed a zero-inflated Poisson regression with random effects for counting outcomes. The parameters in these models were estimated by maximum likelihood. In this paper, as alternatives to maximum likelihood approaches, we will propose Bayesian estimation methods for both the two-part model and the zero-inflated Poisson regression with random effects. The Bayesian methods are more flexible and can be easily implemented in the existing software, R and WinBUGS. We will also present the results from simulation study and real data analysis comparing the standard methods and the proposed methods in the longitudinal adolescent substance abuse study.

C:17

Consistency of Signal Measures with Epidemiologic Effect Measures

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Purpose. As tools for the signal detection on large spontaneous reporting databases, several signal measures, such as the proportional reporting ratio or the reporting odds ratio, are utilized. While these signal measures have similar forms to the epidemiologic effect measures, it is anticipated that the actual risk to subjects cannot be known through these measures because of the nature of spontaneous reports. The objective of this study is to investigate the conditions for the consistency of signal measures with epidemiologic effect measures like the incidence rate ratio. Practical methods to examine such conditions with real data are also proposed.

Methods. Each signal measure is expressed as a function of the time dependent factors: the size of a cohort; the proportion of subjects exposed to drug; the hazard of adverse event; the reporting proportion of a drug-event combination. Under the proportional hazard assumption, the conditions for the consistency of signal measures with the incidence rate ratio are examined. As a numerical example, anaphylaxis related events among quinolones are investigated.

Results. We derived four conditions for the consistency of signal measures. Two conditions are common for all measures: the incidence of the other events is equal between the drug of interest and the other drugs; the odds ratio of reporting proportion equals one. The example suggests the conditions may not hold in real data.

Conclusions. Each signal measure has its own conditions for consistency with the incidence rate ratio. These conditions could be utilized to infer the actual risks through signal measures.

C:18

An Independent Statistical Center in Support of the Data and Safety Monitoring Board: The Adenoma Prevention with Celecoxib (APC) Trial

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The role of an independent statistical analysis center in support of data and safety monitoring boards in the industry-modified National Institutes of Health model has been previously described in general terms . The importance of the data and safety monitoring board in continuing review of ongoing clinical trials to ensure the safety of participants and the validity and integrity of the data has now been widely recognized both by the regulatory agencies and industry sponsors. In order to ensure confidentiality and integrity of interim data review, an independent statistical center is often established by the sponsor in support of the data and safety monitoring boards. Celebrex (celecoxib) and Vioxx (rofecoxib) are both a nonsteroidal anti-inflammatory drug specifically inhibiting cyclooxygenase-2 and were approved by the US Food and Drug Administration, respectively, in December 1998 for treatment of arthritis and in May 1999 for treatment of arthritis and acute pain in adults. The National Cancer Institute launched the Adenoma Prevention with Celecoxib (APC) trial in November 1999, and shortly afterwards Merck launched the Adenomatous Polyp PRevention On Vioxx (APPROVe) trial in February 2000. A regularly scheduled review of the interim safety data from the APPROVe trial by its external safety monitoring board led to a voluntary withdrawal of Vioxx on 30 September 2004 , and this was followed by early termination of the APC trial on 17 December 2004 . In this presentation, the APC trial will be used as an example to illustrate the necessity and the importance of the independence of the statistical center in support of the data and safety monitoring board.

C:19

An Improved Estimating Method of QT Interval for Adjusting Heart Rate: a Multivariate Approach

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Prolongation of the QT interval on a electrocardiogram(ECG) is a key marker for potential cardiac disease. There are several empirical proposals in the literature for adjusting QT intervals for heart rate(for example, Bazett, Fridericia and Sagie correction method, etc). From a statistical perspective, these approaches have been criticized as they tend to overcorrect the QT interval.

On ECG tracing QT interval is defined as the amount of time between the initiation of the QRS complex and the conclusion of the T wave(QT interval=QRS complex + ST interval). The QT interval is highly correlated with heart rate, the conventional correction formulas adjusted on the whole QT interval, which made overcorrection. The QRS complex of the ECG corresponds to the initiation of the contraction. In this period, muscle was relaxed and repolarization of cellular membranes followed. However, we observed the QRS is less associated with heart rate than ST interval.

Motivated by the difference in the degree of the association with heart rate, we proposed multivariate modeling of ECG waveform and derived improved QT correction formula. We used population based cohort study data in Korea, ongoing 10 year follow up study for a model construction and simulation studies were performed to compare to conventional correction methods.

C:20

A Sensitivity Analysis allowing for All Possible Selection Processes of Studies in Meta Analysis

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Meta analysis is now a popular method to obtain more strong evidence in medical research. However, one crucial problem in meta analysis is publication bias, that is, the process of study selection is not usually random, so the overall result may be biased if we neglect it. A popular way to deal with publication bias is to introduce a selection function to the analysis, which describes the probability that each study is selected for review. However, the choice of the selection function is often problematic because it requires strong assumptions which are not verifiable from the available data. In this paper, we consider confidenceintervals and P-values allowing for all possible selection functionswhich satisfy the weak assumption that large studies are as likely, or more likely, to be selected than small studies. The confidence interval and P-value are determined for each given number of unpublished (or missing) studies, so each of these leads to a (worst-case) sensitivity analysis by controlling for it. Using our method, we re-analyze the data used in the meta analysis of Hackshaw et al. (BMJ, 1997) on the lung cancer risk of passive smoking. The possibility of publication bias in this example has been a matter of some dispute in the literature: our analysis shows that although study selection would imply that the relative risk has been exaggerated, it is unlikely to be sufficientto negate the main conclusion in Hackshaw et al. (1997) that passivesmoking does pose a health risk, albeit at a more modest level thanhas been claimed. This talk is based on our recent paper Henmi et al. (2007).

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C:21

Sample Size Allocation to Regions in a Multiregional Trial

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The objective of a multi-regional bridging trial is to show the efficacy of a drug in various global regions, and at the same time to evaluate the possibility of applying the overall trial results to each region. However, to apply overall results to a specific region, the result in that region should be consistent with the overall results or the results of other regions. This article discusses methods of sample size allocation to a sepcific region and regions overall by introducing statistical criteria for consistency between regional and overall results. Specifically, three rules of sample size allocation are discussed: (1) allocating equal size to all regions, (2) minimizing total sample size, and (3) minimizing the sample size of a specific region. Some total and regional sample sizes calculated under each allocation rule are illustrated.

P:01

Bayesian Predictive Multi-stage Design for Phase II Single-arm Clinical Trials:A Case Study

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Phase II clinical trials are an important step through the development of new therapies. These trials are typically small to moderate size exploratory studies to assess whether a new drug or procedure is sufficiently promising to be evaluated in a randomized phase III trial. Ethical concerns that a trial must be stopped early if the experimental treatment seems to ineffective and/or unsafe have led to the development of sequential or multi-stage designs for phase II trials.

A single-arm clinical trial for evaluating the donor-specific transfusion (DST) on living donor liver transplantation is ongoing in Kyoto University Hospital. The primary endpoint is acute rejection on recipients within 6 months after transplantation and the "response" is defined as no acute rejection. We use a beta distribution with hyper parameters (a=1 and b=1) as a prior distribution. The planned maximum sample size is 35, which was determined by the feasible number of patients. The minimum sample size is 10, which was determined based on a minimum level of information to evaluate safety. A maximal response probability threshold is 0.75, based on the investigators' opinions. A minimal response probability threshold is 0.55, which was estimated based on a historical dataset deriving from 155 recipients. In stopping rule for efficacy, the cumulative response probability is based on the maximal response number threshold being 26; If this cumulative probability is higher than 0.80, we will recommend stopping the trial for efficacy. In Stopping rule for inefficacy, the cumulative response probability is based on the minimal response number threshold being 19; If this cumulative probability is higher than 0.80, we will recommend stopping the trial for inefficacy. Six interim analyses are planned. To assess operating characteristics of the design, we did some simulations. The simulation results show that the Bayesian design could provide acceptable type I error rate and moderate power from the frequentist point of view.

In recent years, Bayesian approaches have been applied to complex statistical modeling in biomedical field and several approaches to study designs and monitoring have been proposed mainly in cancer clinical trials. Recently, the CDRH of U.S. FDA released draft guidance for industry named "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials". This guidance shows how Bayesian approaches take more places in clinical trials and it should have a major impact on future clinical development strategies for medical products including devices and drugs.

P:02

Hypothesis Test under the Additive Hazards Model

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In this research, we derive test statistics using the nonparametric likelihood principle under the additive hazards model for the right censored data. We will note that the proposed test statistics are the weighted or generalized log-rank statistics. The derivation of the corresponding variance will be based on the permutation principle. Then we illustrate our procedure with an example.

P:03

Study on the Criterion for Selecting the Working Correlation Structure in Generalized Estimating Equation

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We often handle data that includes repeated observations of one response variable that are correlated to each other for the same individual. Liang and Zeger (1986) proposed the generalized estimating equation (GEE) method to analyze such data, which can be used without strict assumptions on the joint distribution of repeated observations.

The primary role of the GEE method is to estimate parameters in the distribution, and it is necessary to specify the working correlation structure. When an inadequate structure is chosen, the variance of estimators increases, as compared to the case when the ideal structure is selected, i.e., the relative efficiency descends as pointed out by Sutradhar and Das (2000). Consequently, providing an objective criterion for selecting an appropriate working correlation structure is important and useful.

In this paper, we propose one particular criterion for selecting a proper working correlation structure, based on a test statistic for testing the hypothesis that the covariance matrix is a given matrix.

As a result of our evaluation of the proposed criterion by a simulation experiment in the scenario of a two-group comparison, we confirmed that the criterion could enable the selection of the most appropriate correlation structure with a substantially high probability. In fact, the achieved proportion of selecting the true correlation structure fell within the range of 30.8% and 99.1%, depending on the sample size, number of time points, and true correlation coefficients. Interestingly, even when the true correlation structure was not selected with the proposed criterion, the descent of the relative efficiency, which is defined by the ratio between the variance of estimators given by the true correlation structure and that by the proposed criterion, was at most as small as 2%. Therefore, the proposed criterion appeared to be satisfactory for the analysis of actual data. We also examined the practicability of the proposed criterion by applying it to clinical trial data and confirmed that it yields a reasonable result.

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P:04

Statistical Method for Evaluating the Efficacy of a Drug for Osteoporosis on the Occurrence of Bone Fractures as the Primary Endpoint

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Consider clinical trials for evaluating the efficacy of a test drug for osteoporosis compared to a control drug with the occurrence of bone fractures (events) as the primary endpoint. The events are generally identified by periodical checks conducted almost once a year; consequently, the time to event is interval-censored. The duration of trial is usually required to be 2 or 3 years to obtain adequate events. The sample size is usually 1,000 or more, considering dropouts due to such a long duration trial.According to our experiences of clinical trials, the results by two analysis methods, i.e., Poisson regression test (for the number of events) and log-rank test (for the time to the first occurrence of events) provided considerably different results, which motivated us to examine which was more appropriate for our data through Monte-Carlo simulation experiments.The probabilistic models used in the simulation experiments were set by referring to the two clinical trials. The number of bone fractures showed overdispersion beyond the Poisson rule such that negative binomial (Poisson-gamma) distribution was assumed for generating simulation data. Assuming the interindividual Poisson parameters change with a gamma distribution, we set the parameter values of gamma distribution. For the comparison, we used type I error rates and powers as the indices, where the Poisson regression test was adjusted by the estimated magnitude of dispersion. The number of repetitions in the simulation was 10,000 and 1,000 for type I errors and powers, respectively.Concerning type I error rates for a nominal 5% significance level, slightly liberal values such as 5.2% or 5.4% were observed in the Poisson regression test with adjustment of overdispersion, whereas they were below 5% in the log-rank test. Concerning powers, the former achieved a considerably higher value than the latter, the difference being the order of 10%.Since the increase of power of the Poisson regression test was sufficiently greater than the negligible increase of type I error rates, we recommend the Poisson regression test with adjustment of overdispersion rather than the log-rank test, to compare the drug efficacy on the occurrence of bone fractures between treatment groups. References:Metcalfe, C. and Thompson, S. G. (2006). The importance of varying the event generation process in simulation studies of statistical methods for recurrent events. Statistics in Medicine, 25,165-179.Keywords: osteoporosis, bone fracture, Poisson regression, statistical method, adjustment of overdispersion, log-rank test, negative binomial distribution

P:05

Study on the Effect of Random Effects included in the Analysis Model for In Vitro Pharmacological Data Adaptable to Four Parameter Logistic Model

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Our interest lies in the estimation of parameters in a 4 parameter logistic model assumed on the data obtained in *in vitro* pharmacological experiments with the objective to identify the concentration-response relationship. The functional form is essentially assumed to be $f(d) = -\beta_3+(\beta_4-\beta_3)/(1+(\beta_4 \exp_{10} (\beta_2 (\beta_1-d))/ \beta_3)$, where d is the concentration and β_1 and β_4 are the 50% inhibition dose (IC50) and the maximum response, respectively. We considered the cases where a response is observed on individuals at all of the certain number of doses and the parameters are variable depending on individuals as the true state of nature.Two issues were addressed in this study; the one is to identify an appropriate estimation method and the other is to determine the model for analysis which might not be the true model. We took a standard two-stage method (STS), a first order approximation method (FOA), a Laplacian approximation method (LAP), a Monte Carlo integration method (MCI), and an adaptive Gaussian quadrature method (GAU) as the methods for parameter estimation to be compared. Eight cases to assume random effects on parameters were considered as the model for analysis.Estimation methods and models for analysis were compared using Monte-Carlo simulation experiments. The performance was evaluated through the convergent rate, bias, and discrepancies of 2.5 and 97.5 percentiles from the true value.The result of simulation showed that STS and FOA achieved a high proportion of convergence in the sequential approximation for estimation. LAP, MCI and GAU achieved a considerable proportion of convergence only when few random effects were assumed in the model for analysis. In a model which assumed random effects on the parameters for β_1 and β_4, the performance of interested parameter β_1 was similar without FOA. The convergent rates in parameter estimation of this model were 95% or more at any methods. For this model, the performance of other parameters was able to improve more than STS. Moreover, LAP, MCI, and GAU were able to be estimated the same performance in this model. The result of simulation experiments suggested that LAP which assumed random effects on the parameters for β_1 and β_4 should be used in the analysis irrespective of the existence of true random effects. Reference1. Finney, D.J. (1983). Clinical Chemistry 29, 1562-1566.2. Steimer, J.L., Mallet, A., Golmard, J.L., and Boisvieux, J. F. (1984). Drug Metabolism Reviews 15,265-292.

P:06

Statistical Analysis of Spatial-time Heterogeneity of Cancer Mortality Risk based on Growth Curve Model

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It is considered that disease risk, which is usually quantified by incidence or mortality, may have some regional chronological change patterns due to change of environmental factors such as exposure-level and custom of residents. For cross-sectional studies, the Poisson regression model was commonly used. The random effect models were also proposed in consideration of regional heterogeneity. The purpose of our study is to develop a reasonable statistical method for analyzing regional heterogeneity on the time trend of cancer mortality risk and searching factors which contribute to such heterogeneity. In this paper we propose a statistical model for describing the regression relationship between the responses with continuous type of error obeyed normal distribution for basics and the explanatory variables by combining the Poisson model and Vonesh-Carter-Ohtaki type growth curve model ([4],[5]). The proposed model was applied to prefecture-specific mortality data of large bowel cancer during the period from 1975 to 2002 in Japan, where the response and the main explanatory variables were logarithmic transformed standardized mortality ratio and calendar-time, respectively. Some geographical, demographical, sociological and environmental factors were selected as covariates. From the result of analysis, the male's mortality risk was significantly increasing, stopped increasing at 1993 and has been flat from 1993 onward. On the other hand, the female's mortality risk was increasing and begun to decreasing at 1991, and has been decreasing significantly from 1991 onward. Further, metropolitan or areas having low sunshine exposure were high mortality risk for both sexes. In particular, it seems that the gap between the metropolitan and rural area are decreasing across the years. The effect of sunshine exposure on mortality risk has been thought that the sunshine exposure produces a vitamin D in the skin and vitamin D reduces the risk of cancer ([1],[2],[3]).

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P:07

Modified Cp in Multivariate Ridge Regression

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The method of ridge regression, proposed by Hoerl and Kennard (1970), attempts to overcome the problems of multicollinearity between explanatory variables. The basic idea is shrinkage of the parameter space by using a ridge parameter and it is a continuous dimension reduction of explanatory variables. In the sense, variable selection problem on ridge regression is more flexible than discrete variable selection on existing linear regression. The best ridge parameter might be selected or optimized by minimizing Cross-Validation type criterion based on mean square error, which is an estimator of underlying risk function. However those CV type estimators, for example GCV (Li, 1985), have constant bias when the number of sample size is small. Therefore a better variable selection criterion on rige regression is desired.

Cp-statistics (Mallows, 1973) is one of the most popular variable selection criteria on linear regression. Fujikoshi and Satoh (1997) modified it and proposed MCp as an unbiased estimator on multivariate linear regression under normally distributed error. Davies, Neath and Cavanaugh (2006) proved that MCp was a minimum variance unbiased estimator. In this paper MCp is extended to multivariate ridge regression and a new variable selection criterion is proposed. Its properties are investigated analytically and numerically.

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P:08

Multinational Clinical Trials in East Asia

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Background With the merge and acquisition of pharmaceutical industries, many pharmaceutical giants have been extending their cooperation worldwide. The internationalization and globalization of new development becomes inevitable, and multinational clinical trials (MNCTs) in east Asia are increasing. There are, however, still few reports on the actual status. The purpose of this paper is to analyze the status of MNCTs in east Asia by using a clinical trial registry database. Methods "ClinicalTrials.gov" provides regularly updated information about federally and privately supported clinical research in human volunteers. It is the biggest clinical trial registry database all over the world. The worldwide information on clinical trials was collected by using "ClinicalTrials.gov", and all data about east Asia were picked up from it. Results The numbers of clinical trials, which are recruiting patients now, were 321 in Japan, 260 in China, 99 in Hong Kong, 526 in Taiwan, and 283 in Korea, respectively. Among them, the numbers of clinical trials supported by industry were 196 in Japan, 137 in China, 78 in Hong Kong, 166 in Taiwan, and 205 in Korea. In China, the partners of MNCTs supported by industry were from the US in 49 trials, from Hong Kong in 45, from Taiwan in 42, from Korea in 42, and from Japan in 4. In Japan, the partners of MNCTs supported by industry were from the US (12), China (4), Hong Kong (5), Taiwan (8), Korea (10), and so on. For Korea and Taiwan, most of the trials (81) were conducted in collaboration with each other, besides in collaboration with the US (Korea 92 and Taiwan 77). As mentioned above, the numbers of MNCTs were the least in Japan Compared with China, Korea and Taiwan. Conclusion MNCTs have spread throughout most countries in east Asia, where the patient population is large and the trial cost is relatively low. East Asia is a market worthy to be developed. Japan has being left behind in the flow until now. But it is expected that MNCTs conducted by Japanese company will increase rapidly, because the Japanese guidance of MNCT was published in September of 2007 and Japanese government is now encouraging MNCTs.

P:09

Two Dimensional Summarization for Affymetrix GeneChip Probe Level Data based on Functional States of Gene-ON/OFF

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Motivation

The Affymetrix GeneChip (PM, MM) probe pair is designed with the intention of measuring non-specific binding. The removal of non-specific binding or cross-hybridization signal from a PM measurement is a key issue in the analysis of microarray data. Many researchers have pointed out that direct subtraction of MM from PM is unlikely to be useful, because MM contains mostly target-specific signal as well as PM. As for methods for summarizing probe intensities in a single index, numerous model-based algorithms have been proposed, however the most algorithms are too complicated with many parameters having poor biological implication. Biologists who want to analyze GeneChip microarray data might be bewildered with the availability of so many procedures with varying results.

Purpose

To provide a model-based algorithm for summarizing prove level data into indexes: (summarized intensity, probability ON)

Material

Human Genome U95 data set was used for analysis. It consists of a series of genes spkle-in at known concentration.

Statistical analyses

(1) Summarization of intensity

A principal component analysis was applied to the data set to explore the most important aspect of data. A gene expression intensities adjusted by probe affinity, was mostly explained by the first principal component. The contribution of PM variables to the first component was almost the same each other. The same went for MM variables.

(2) Probability ON/FF

Assuming two separate functional states of a gene: ON/OFF, we gave a mathematical basis for the pair of measurements (PM, MM) based on the hypothesis that PM and MM have the same distribution when a gene is in the OFF state. Let X be the number of pairs in a probe set satisfying MM&gtPM. The probability of a gene being ON under the condition X=x was estimated.

Conclusion

A feature of gene expression was summarized into a pair of indexes: one was a summarized intensity of probe set using a principal component analysis and the other was the probability a gene being ON using the number of times MM&gtPM per probe set. The validity of proposed summarization method was examined using Human Genome U95 data sets. The probability a gene being ON/OFF is useful to discriminate specific bindings from non specific bindings.

P:10

Effects of Lifestyle Modification on Metabolic Syndrome: Resolution Rate and Combining Multiple Endpoints in Meta-Analysis

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The metabolic syndrome, also called insulin resistance syndrome or syndrome X, is a high-risk state for diabetes and cardiovascular disease. It is a combination of medical disorders related to the conditions includes type 2 diabetes, obesity, high blood pressure, and a poor lipid profile with elevated LDL cholesterol, low HDL cholesterol, and elevated triglycerides. It has been identified as a target for lifestyle modification to reduce risk of cardiovascular disease; however, the effects of lifestyle modification are still uncertain. In this paper we consider a meta-analysis on the effect of lifestyle modification on metabolic syndrome and its component. When several clinical trials report multiple outcomes, meta-analyses ordinarily analyze each outcome separately. We analyze the several outcomes jointly with several models; compare the results with the multivariate meta-analysis as well as the standard univariate approaches examined by fixed-effects model, random-effects model and Bayesian model with non-informative priors using MCMC.

This meta-analysis provided evidence of the efficacy of lifestyle education for individuals of metabolic syndrome patients in reducing RD of the resolution rate. The risk of metabolic syndrome in the lifestyle education intervention group was reduced approximately by 30% [RD= 0.29, 95%CI: 0.16 to 0.42]) compared to the control intervention group by the random-effects model. As for each component, 5 components excluding TG were significantly reduced in the lifestyle education groups compared to their control groups by the simple meta-analysis, however, only brad pressure index (SBP and DBP) denoted significant effects by the multiple meta-analysis.

Lifestyle education was effective for reducing both prevalence of metabolic syndrome as well as related abnormality for metabolic syndrome in metabolic syndrome subjects and may be a useful tool in reducing metabolic syndrome.

P:11

A New Feature Extraction Method from very Non-normal Data: Analysis of Multivariate Catch and Bycatch Data by Purse-seine Tuna Fisheries

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We propose a new feature extraction method for very non-normal data that generalizes principal component analysis in the same manner as generalized linear model. As a specific model, we introduce generalized PCA with a Tweedie distribution and analyze multivariate catch and bycatch data in purse-seine tuna fisheries.

P:12

Statistical Pharmacokinetic Modeling of Controlled-Release Analgesics Combining Immediate-Release and Sustained-Release Components to Design an Appropriate Drug Delivery

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In pharmacokinetics, which investigates the processes of drug on in vivo absorption, distribution, metabolism and elimination, the method for estimating pharmacokinetic parameters to the basic compartment models has been established. However, as for formulations with multiple absorption processes, modeling and estimation methods for pharmacokinetic parameters have not still been sufficiently examined. Actually WinNonlin, the standard software widely used for pharmacokinetic analysis does not cover such a method. On the other hand, clinically there is much demand for sustained-release analgesics, which control the release rate of drug, combining two-strata; immediate and sustained release components. Sustained-release analgesics that is, they can raise blood drug concentration rapidly and can retain over a specific level of blood concentration for a long time are strongly required to patients. Thus, it is necessary to investigate an appropriate pharmacokinetic model and an estimating method for its parameters in controlled-release formulation. Also, regarding the ratio of combination for the immediate and sustained release components, it has been required to investigate the clinically most appropriate ratio based on the statistical model in the drug development. In this study, the pharmacokinetic compartment model for controlled-release type analgesics was applied, followed by calculating estimated values of blood concentration from the model formula, and the fitness of the model to measured values was investigated. Based on the compartment model, the pharmacokinetic parameters were estimated. Due to a concern about interindividual difference in the compartment model, some random effects was added using a non-linear mixed effect model. Also, it was investigated whether or not the basis for deciding the combination ratio of the immediate and sustained release components had been practical to the actual data. In order to do that, firstly, time changes of blood concentrations of the immediate release component only and the sustained release component only, which were the same dosage, were derived by a simulation based on the calculated pharmacokinetic parameters. Then, the basis for deciding the combination ratio of the immediate and sustained release components was explored. Secondly, it was validated whether the basis had been put into practice in the actual data using the compartment model in controlled-release type formulation. Moreover, it was investigated whether the more appropriate ratio could have been considered by changing the immediate and sustained release components-combining ratio. These details will be presented in the conference.

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