Features:

Interview with a Distinguished Mathematician
Candidates of ICSA Officers
Special Feature Article: Financial Econometrics
Controversial Statistical Issues
Meeting Announcements
Highlights of 2005
Applied Statistics Symposium
From the Editor
Kao-Tai Tsai, Ph.D.

It seems like yesterday when I received the email from the Chair of the Publication Committee to inform me that I had been elected to be the Editor of the Bulletin for the next three years. Now, I am putting together the last issue during my tenure as the Editor with lots of mixed thoughts.

The ICSA had good growth in the past three years according to the reports published in the previous issues of this Bulletin. More of our members had been recognized for their outstanding achievements. The Applied Statistics Symposium had become an important conference judging by the number and the quality of sessions each year. In addition, our organization had been more actively reaching out to other professional organizations. On the other hand, with somewhat of a sad note, a few great friends of the ICSA had left us and passed on to eternity.

Just like anything in life, we can not rest on our laurels and become too complacent. We still have lots of room for improvement. The number of members had little growth in the past three years. Many ICSA committees could have been more active to serve the organization, and we still need to recruit new blood to establish a broader membership base for the future growth and to better serve our members.

In this issue, in addition to the regular reports of the ICSA business and activities, we had the privilege to interview Professor Yau of the Harvard University. His insight and his life experience set a unique model for many of us. His great effort to build up the advanced mathematical research in China deserves not only our admiration but also our support. We also have Professor Fan of Princeton University introducing the area of research in financial econometrics. Of course, the controversial statistical issues always remains as a popular column.

From next year, Professor Kao of the Uniformed Services University will be the new Editor for the Bulletin. I sincerely encourage everyone to support him as much as you can. As I have said many times previously, no editor can accomplish much without the strong support from the members.

As usual, we hope you enjoy the fruit of our labor in this issue. Your help and contribution in the past three years had always been greatly appreciated. On behalf of the editorial team, I would like to sincerely wish you all the success in life.

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ICSABulletin, July 2005

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Submission Guidelines
ICSABulletin

Articles
The ICSABulletin welcomes the submission of articles by the members. Articles submitted should be written in traditional Chinese or English. The contents should be aimed at the general reading.

Articles can be submitted electronically or in print. If submitted in print, please leave ¾ inches of blank space on each margin of the letter size paper. The font size of 11 or 12 with Microsoft Word is preferred when typing.

Submission deadline for the January issue is December 15 and the deadline for the July issue is June 15. Articles received after the deadline will be published in the following issue of Bulletin.

Advertisements
The ICSABulletin welcomes the submission of advertisements related to the profession of Statistics. The fee for a whole page advertisement is US$300.00. Please contact the Editor for the fee schedule of advertisement with other sizes.

Questions
Please submit your questions to the Editor by email at tsa0123@yahoo.com.

For the complete list of Committee Members and terms, please go to the ICSA website: www.icsa.org.
From the President
Jiahua Chen, Ph.D.

The official opening activity of the board of directors and committee chairs of year 2005 was a telephone conference held on February 8th. Majority of the board members and committee chairs participated in the conference and used the opportunity to get to know each other. A number of issues were raised in the conference. Some of the issues were addressed right away, some were carried on and resolved afterward, and yet some others have still been in progress with extended discussion.

When I am preparing this message, the ICSA Applied Statistical Symposium (June 12-15, 2005) is under its way to start in the metropolitan area of Washington DC. The next Applied Statistical Symposium will be held in June 14-17, 2006. University of Connecticut at Storrs, Connecticut. A subcommittee has been working on all the logistics for the next symposium, including the academic programs, fund raising, banquet arrangement, and tour. See a tentative program plan in this issue of the Bulletin. I strongly urge everyone to mark your calendar and make effort to take part in the 2006 ICSA Applied Statistical Symposium.

The Nomination Committee chaired by Dr. Xuming He started soliciting nominees in early this year. The quality and efficiency of their work has been very impressive. By the time of writing this, the committee has secured a well-diversified and representative list of candidates. The list is expected to be approved by the board during a board meeting during the Applied Statistical Symposium in DC this month. Please see the information on the candidates published in this issue of the Bulletin and be sure to exercise your right to vote at your earliest convenience. On the other hand, the nomination committee and I continue to believe that we might have under-utilized the intelligence pool of our members. If you have not been asked to

serve in the ICSA board so far, please make yourself ready and the ICSA radar screen may soon spot the cross on you.

The board has recently approved that the ICSA be listed as a reciprocal society of the American Statistical Association. To the benefit of our members residing in the North America, you are entitled a $10 reduction of the ASA membership. The ICSA members residing in the Asia-Pacific regions qualify for further reduced membership dues. Please refer to the open letter jointly by the presidents of ICSA and ASA sent to you earlier electronically, and published in the bulletin to find how you might be able to benefit from this agreement as a member of the ICSA and the American Statistical Association.

The ICSA has been considering upgrading our webpage and increasing its functionality. At this moment, we are in urgent need of more volunteers talented in website design and maintenance. The ICSA has relied on the utterly selfless help from Dr. Don X. Sun in the past and is counting on his continued loyalty. As the ICSA is turning to high-tech for our daily operation, the workload surely needs to be shared. Suggestions on how to re-design our website will also be very much appreciated. Please contact any of our board members for comments and suggestions.

The coming JSM to be held in August 7-11, Minneapolis, Minnesota will be another good opportunity for ICSA members to interact with each other. Professor Wenlian Li and his colleagues at University of Minnesota have arranged our annual banquet jointly with a cruise. If you are to attend the JSM, be sure to purchase tickets early to secure seats. ICSA will set up a booth at the JSM for ticket sell and for promotion of our society. As usual, the booth will also be used to attract new members. Please stop by the booth to meet with your old and new friends and bring some prospective ICSA members to the booth.

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INTERNATIONAL CHINESE STATISTICAL ASSOCIATION YEAR 2005
APPLIED STATISTICS SYMPOSIUM

泛華統計協會

Dear ICSA member:

Working together as the leaders of two important statistical societies, we want to inform you of a new reciprocal partnership between the International Chinese Statistical Association (ICSA) and the American Statistical Association (ASA). As a current ICSA member, you are eligible to join the ASA as a new member at one of two special discounted rates:

- ICSA members residing in the Asia Pacific Region including Mainland China, Hong Kong, Taiwan, Singapore and others (see www.amstat.org/membership/devcountry for other eligible countries), may join the ASA as full members for only $35 (U.S.) per year. This special rate includes online access to the Journal of the American Statistical Association (JASA), The American Statistician (TAS), and the Journal of Business and Economic Statistics (JBUS) at no additional cost!

- ICSA members residing in all other countries may join the ASA as a full member for only $75 (U.S.) per year, a $10 savings off the ASA's regular membership dues. This membership includes a one-year subscription to Amstat News, the ASA's monthly membership magazine and a variety of other member benefits.

Becoming a member of the ASA is a great way to enhance your statistical practice and to gain access to a network of over 17,000 statisticians throughout the world. ASA members enjoy a wide variety of benefits, including:

- Expanded Career Horizons with ASA's online JobWeb, annual JSM Career Placement Service and monthly job postings in Amstat News;
- Discounts of all of the ASA's Products & Services including a wide variety of peer-reviewed journals, magazines, newsletters, proceedings, and brochures;
- "Members Only" Registration Rates for the Joint Statistical Meetings, an annual gathering of over 5,000 statisticians professionals sharing research and new developments;
- Free Online Access to the Current Index to Statistics (CIS), a bibliographic index to publications in Statistics and related fields, and much more!

Since 1839, the ASA has been the leading forum for members of the statistical community to share ideas, new methods, problems, and solutions. For more information about ASA benefits and why over 17,000 members worldwide consider ASA membership essential, please visit our website at www.amstat.org.

If you would like to take advantage of this special offer, please complete and return the enclosed form at your earliest convenience. If you have any questions, contact us by calling (1) (888) 231-5473 or emailing gaiaminfo@amstat.org. We look forward to welcoming you into the American Statistical Association.

Sincerely,

ICSRA President & ASA President

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From the Executive Director
Ivan S.F. Chan, Ph.D.

The 2005 Applied Statistics Symposium was held in a state-of-the-art conference center in Bethesda, Maryland during June 12 to 15. It was another continued success with a strong program that attracted a large number of participants. I would like to extend my sincere thanks to the symposium committee (with Yi Tsong as the Symposium Chair and Jim Hung as the Program Chair) for their tremendous efforts in making this meeting a wonderful experience.

This year we will elect several officers, including 2006 President-Elect, 2006 Biometrics Section Chair, and 6 Directors of the ICSA Board (2006-2008 term). I would like to thank the Nomination Committee, under the leadership of Xoming He, in selecting a list of very strong candidates. By now you would have already received the ballot (if not, please check the website or contact me), and I urge all of you to participate in this important event and cast your vote. Your input is critical in selecting the future leaders of ICSA. The results of the ballot will be reviewed at the board meeting at the JSM in Minneapolis and announced at the Annual Members Meeting on August 11, 2004.

If you are planning to attend the Joint Statistical Meetings (JSM) in Minneapolis, Minnesota (August 8-12), be sure to visit the ICSA booth to find out what is new in ICSA and to meet new and old friends. ICSA and Statistica Sincera also co-sponsored an invited session on “Statistical Analysis for Brain Imaging” to be held on Sunday (August 7), 2:00 to 3:50 PM. Please also plan to attend the Annual Members Meeting on August 10 (Wednesday, 5:30-6:30 PM, Convention Center, MCC-103A). Following the Annual Members Meeting, please join us for a dinner cruise along the beautiful Mississippi river. Please see the separate announcement in this bulletin for details regarding the dinner cruise. We sincerely thank the Local Organizing Committee (chaired by William Li) for coordinating these important activities.

Finally, I would like to ask you to please take a moment to check your membership information at the ICSA web site and make necessary changes if the information on the web is outdated. Please also provide your e-mail address if you forget to do so previously. Having your updated e-mail addresses would allow us to disseminate information and communicate with you in a timely manner. If you do not remember your login ID or password, please contact Jun Zhao (Membership Committee Chair, e-mail: jzhao@organonusa.com) or me (e-mail: Ivan.Chan@Merck.com).

I look forward to seeing you at the JSM, and I wish all of you a great summer.

Ivan S. F. Chan, Ph.D. is Director of Clinical Biostatistics at Merck Research Laboratories.
Email: Ivan.Chan@Merck.com
Program Committee
By: Naitee Ting, Ph.D.

There are three very important ICSA programs during 2005: the annual Applied Statistics Symposium at Washington DC, the JSM membership meeting and banquet in Minneapolis, and the MCP2005 (Multiple Comparison Procedure 2005 International Meeting) at Shanghai. We hope to see you in all 3 programs. If you can't make to all 3, we encourage you to participate in at least one, or may be two of these impressive events.

The 2005 ICSA Applied Statistics Symposium takes place between June 12 and 15 at Washington, DC. Dr. Yi Tsong from the FDA chairs this symposium. Please go visit our web www.icsa.org for more details.

During the August Joint Statistical Meetings at Minneapolis, there will be ICSA business meetings, and there will also be a membership meeting, and the annual banquet. Both the membership meeting and the banquet will take place on August 19th. These activities are planned and organized by Professor William Li at University of Minnesota. Please refer to Professor Li's article in this bulletin for more details.

For the MCP2005, ICSA serves as a co-sponsor. MCP2005 will be held in Shanghai from August 17 to August 19. Dr. Jason Hsu and Dr. Ajit Tamhane co-chair this event. For more details, please visit http://www.stat.ohio-state.edu/~mcp2005. We encourage all ICSA members to support MCP2005.

Looking into the future years, ICSA will have very strong programs in 2006 and 2007. The 2006 Applied Statistics Symposium will take place at University of Connecticut, Storrs, CT in June 14-17, 2006. This symposium will be co-organized by Dr. Greg Wei and Professor Ming-Hui Chen. Please see article prepared by the ICSA 2006 Applied Statistics Symposium organizing committee in this bulletin.

The program committee proposes to hold the seventh ICQSA International Conference at Taiwan in 2007. This conference will be coordinated by Ching-Shui Cheng. The program committee proposes to hold the 2007 Applied Statistics Symposium at North Carolina, to be co-organized by Shu-Yen Ho and Danyu Lin.

Naitee Ting, Ph.D. is an Associate Director in Biostatistics, Pfizer Global Research & Development, New London, CT 06320, USA
Email: naitee.ting@gretna.pfizer.com.

Report From Symposium Committee Chair
By: Yi Tsong, Ph.D.

Shou-Hua said: "Well, it looks like our mission is accomplished. It is a quite successful symposium." I looked around and seeing every attendee was getting ready to leave. Between the "Have a nice trip!" and "See you at UCON in 2006!" I hesitated but finally managed to utter back to Milton and Shou-Hua, "I guess it is safe to say that now".

A few minutes later, we turned around and congratulated our young statisticians for their contributions to this symposium and heading out to lunch and office. On the way to the restaurant, I can't help but felt joy, relief, proud and grateful.

In 2003 August, when I proposed to organize the 2005 ICSA Applied Statistics Symposium, Jim and I had no clear idea who exactly should we count on to carry out such a task. All we had was the confidence in the symposium series itself and the talents of our colleagues in Washington metropolitan areas. Once we started recruiting members of the planning committee, Jim and I was pleasantly surprised by the enthusiasm of our colleagues. So we started planning with the starting fund transferred from ICSA Symposium general account. The planning was shifted into high speed gear starting right after JSM last year. Assignments came first, Jim Hung took the responsibility of general program scheduling and invited session program; Milton Fan took charge of accounting and registration with help from Lap-Ming Wun, Lap-Wun and Shou-Hua Li took charge of hotel and banquet restaurant scouting; Ai-Yi Liu took charge of contributed paper sessions; Grace Yang took charge of student paper competition; Sue-Jane Wang took charge of Jeann-Ping Hsu memorial session; Ling Chen took the responsibilities of the short courses; Jao-Hai Li would recruit his colleagues and students to manage the registration desk and equipment; Gang Zheng would handle the website, and so on. We started with the interest to hold the symposium at the Marriott Hotel and Conference Center at College Park, Maryland. But when we noticed that a new Marriott Hotel and Conference Center would be built near most of our members' home and office, we were all excited and decided to move to the new hotel. It is proved to be a right move for its convenience to both committee members and participants.

By the end of 2004, the program seemed to be in great shape before the worry of funding grew. One thing we learned about symposium spending is that there is no unbiased estimate of hotel and conference expense. There is only under-estimate. Hence, we recruited Jun Zhao to help out with corporate fund raising. It was later proven a life-saving move. By April of 2005, we found that our announcement in AmStat News didn't come out and the attendance of the short courses was lower than expected. A few members of the planning committee started to worry about our future, even though base on the committed attendees (early registrations, speakers, chairs and organizers, etc.), we knew the attendance would be no less than 200. But we all agreed that it was too late to worry about promotion or changing of the plan. Jim and I have to cheering the committee up by saying "ICSAS has committed to provide fully support to the symposium regardless the cost". "Don't worry, we are doing OK. We are expecting 20% onsite registration" and "Our responsibility and focus is not in breaking the record of attendance but to lift the level of symposium to a level to make the symposium a worthwhile experience for every attendee". By the end of May, we all felt everything was read for "the real thing" now.

Finally, there were about 250 participants showed up for the symposium. On Sunday, June 12th, five courses were offered covering topics such as "quality of life data", "interim and adaptive design", "incomplete longitudinal data analysis", "pharmacoepidemiology" and
"generalized linear latent and mixed models". All courses were lectured by experienced and excellent instructors. On Monday, June 13th, Dr. Scheuren, the President of American Statistical Association open up the symposium with his keynote speech “Outreach to other national statistical societies". In his talk, he proposed the concept of improving communication and collaborative work between ASA and ICSA. On Tuesday, June 14th, Dr. Gordon Lan opened the program with a plenary speech on statistical methods in medical research. The symposium offered 38 invited sessions and 5 contributed paper sessions. With topics covered critical issues in pharmaceutical statistics, quality control, financial and business statistics, genetic statistics, statistical developments in China and Taiwan, Bayesian statistics, and career planning and development. On Wednesday, June 14th, the symposium is wrapped up with an important topic on “How to make a phase III clinical trial successful”.

On Monday, June 13th, attendees enjoyed a Chinese banquet at the Far East Restaurant. The after-dinner karaoke and dancing brought everybody to the festival mood.

Now after a 12 month planning and developing, the symposium is carried out smoothly and the event is over. The experience we shared is both important and unique. I will treasure this experience with pride and gratefulness. I want to say it again to all my colleagues that worked on this symposium project, “I felt honored to work with you on this 2005 ICSA Symposium.”

Candidates for 2006 ICSA Officers

**President Elect - 2006**
Board of Directors (6) - 2006 to 2008

Candidates for 2006 President Elect

**SHAO, Jun**

**[PRESENT POSITION]** Professor in statistics (1996-present), University of Wisconsin-Madison; Consultant for Millennium Pharmaceuticals, Inc. (2003-present) **[FORMER POSITION]** Associate Chair, Department of Statistics, University of Wisconsin-Madison (1997-2004), Covance Senior Research Fellow (1998); ASA/NSF/BLIS Census Bureau Senior Research Fellow (1996-1997);

**[DEGREES]** B.S. in Mathematics, East China Normal University, P.R. China (1982); Ph.D. in Statistics, University of Wisconsin-Madison (1987).

**[FIELD OF MAJOR STATISTICAL ACTIVITIES]** Research in the jackknife, bootstrap, and other resampling methods; model and variable selection; variance estimation and imputation methodology in survey problems; longitudinal data analysis with missing data; bioequivalence; drug shelf-life estimation; and clinical trials.


**[STATEMENT]** I am greatly honored to be nominated as the candidate of president of ICSA. Like many of you, I witnessed all the efforts, services, and selfless contributions of our members that lead to a rapid growth of the ICSA from a small group of faculty and students to an important and well recognized international organization in the statistical profession. I am thrilled by the idea that it is now my opportunity, if elected, to commit my time and efforts to serve for the ICSA. Since its founding, I have shown a long commitment to the ICSA through continuous membership and service. My statistical background is diverse in theory, methodology, and applications, and my experience is international in perspective. I believe strongly that working with all of you we can accomplish our missions for a bright future of the ICSA. To serve you would be a privilege. If elected, I will focus on the following goals as a starting point: (1) I will work on building membership for the ICSA, especially among younger statistical professionals and statistical communities outside of North America. Our goal is to make the ICSA a truly international statistical body to which the entire statistical community will look for leadership and direction. (2) I will use my experience in editorial work to promote *Statistica Sinica* and make it an influential journal in international statistical profession. I will also search ideas in strengthening the ICSA Bulletin to make it one of the most popular and readable statistical newsletters. I will work on the possibility of having
an ICSA applied statistical journal (such as an electronic journal that will complement and enhance the scope and importance of *Statistica Sinica*), if it remains to be an issue at the time I will serve for the ICSA. (3) I will continue to promote the ICSA Applied Statistics Symposium and the ICSA International Conference and make them as significant international statistical conferences for all members and possibly an even wider statistical community. (4) I will try to make the ICSA play a more active role in serving our members’ needs, such as information exchange, placement and research opportunities, and programs that are relevant and valuable to members and potential members. (5) I will support the development of ICSA web service, because it will not only improve communication, information delivery, data warehousing, on-line publishing, election, and membership renewal, but also reduce some major expense of the ICSA.

[WANG, Sue-Jane]

[PRESENTER POSITION] Associate Director, Office of Bioinformatics, Office of Pharmacoepidemiology and Statistical Science, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration.

[ADJUNCT POSITION] Adjunct Professor, George Washington University, Washington DC and Johns Hopkins University, Maryland. Faculty, Statistics, Foundation for Advanced Education of Science, Graduate School, National Institute of Health, Maryland, USA.

[FORMER POSITION] Acting Statistics Team Leader for Division of Gastroenterology and Coagulation Drug Products and Division of Pulmonary and Allergy Drug Products, Expert Mathematical Statistician, Office of Biostatistics, OPASS/CDER/FDA.

[DEGREES] Ph.D. in Biostatistics, University of Southern California, Los Angeles, CA, 1993.

[FIELD OF MAJOR STATISTICAL ACTIVITIES] After joining FDA, her major statistical research and interests include design and statistical methods for noninferiority active controlled trials; adaptive/flexible designs; genomic drug trials and epidemiology methods.

[SELECTED PUBLICATIONS] Dr. Wang’s collaborative research has resulted in more than 50 research articles in peer-reviewed journals (including: Biometrics, Biometrical Journal Statistics in Medicine, Controlled Clinical Trials, Journal of Computational Biology, Pharmacogenomics, Alcoholism Clinical and Experimental Research, Journal of Biopharmaceutical statistics, Molecular and Cellular Probes, American Journal of Medical Genetics, Gastroenterology, a book chapter in methods of microarray data analysis IV, etc.)

[HONORS AND AWARDS] Dr. Wang received ICSA Distinguished Service Award (2004). She received the following awards, among other awards, in FDA: FDA Scientific Achievement Award (2003); FDA Outstanding Service Award (2003).


[RELATED PROFESSIONAL ACTIVITIES] Dr. Wang is a member of ICSA and ASA. Her related professional activities in the various statistical, clinical, bioinformatics, and genomics meetings, e.g., ASA, ENAR, EITC, AAPS, DIA, PhRMA/FDA, NCI, include a member of program committee, planning committee, steering committee; chair, co-chair, organizer, discussant. Dr. Wang also serves as a referee for biostatistics, biometrical journal, statistics in medicine, controlled clinical trials, J. of biopharmaceutical science, biopharmaceutical statistics, Alcohol and Alcoholism. In April 2004, Dr. Wang represented FDA and co-chaired “PhRMa/FDA Genomics (microarray) Biostatistics Workshop”. In April 2005, she co-chaired and co-chaired/ moderated the Tracks of the “Genomics in drug development and regulatory decision-making: workshop III” co-sponsored by FDA, DIA, PWG, PhRMA, BIO. She is currently the CDER Statistics Delegate, Interdisciplinary Pharmacogenomic Review Group at U.S. FDA.

[STATEMENT] I am deeply honored to be nominated as a candidate for the president of the ICSA and I thank the Nominating Committee for this opportunity. My interest in running for the position is inspired by the tremendous efforts and contributions of our fellow members served for the Association throughout their years. With their efforts, ICSA enjoyed all the successes since its inception. We all witnessed the rapid growth of the Association and it is well recognized by our professional colleagues as an important international organization in the statistical profession. With the unselfish contributions and rigorous efforts of our members, ICSA provided many worthy services to its members. These include: *Statistica Sinica*, a statistical journal co-sponsored by ICSA, is a highly recognized journal in our profession. ICSA is one of the most popular statistical newsletters, *ICSAP Applied Statistics Symposium* is one of the major statistical events in United States, *ICSA International Conference* enjoyed its successes every four years, the book and journal donation program makes significant contributions to building up statistical libraries in China, and many more. Presidency of the ICSA is an enormous undertaking. Having served in multiple capacities for the last several years, I wish to continue the fine tradition of our Association that builds strong and broad membership base from academia, industry, research organizations and government institutions and across all geographic regions. I will try my best to continue promote activities that can meet members’ growing needs, strengthen communication within this organization and interaction with others, and increase visibility, not only within the Chinese statistical community but also among non-Chinese statisticians, to continue membership drive, especially among young Chinese statisticians and to coordinate/co-sponsor professional meetings/events with other professional societies (ASA, IMS, regional societies in Asia, etc.). I will also evaluate the possibility of establishing the annual ICSA applied statistics journal through a refereed process based on talks presented in our annual applied statistics symposium or international conference.

Candidates for Board of Directors – 2006 to 2008

CHEN, Yonghua (Jesh)


CHEUNG, Siu Hung


**RECENT INTEREST** Currently active in the area of statistics education: member of the working group of Secondary Mathematics Curriculum, Education and Manpower Bureau, Government of the Hong Kong Special Administrative Region; Investigator, Statistics Area, Project on “Case-Based Learning of High School Science Subjects” supported by the Quality Education Fund, Government of the Hong Kong Special Administrative Region.

**Fan, Mike** Chang-jun 

**PRESENT POSITION** Senior Mathematical Statistician, Division of Biometrics II, Office of Biostatistics, Center for Drug Evaluation and Research, Food Drug Administration, Rockville, Maryland.


**FIELDS OF MAJOR ACTUARIAL ACTIVITIES** biostatistics, clinical trials, logistic regression, meta analysis, non-inferiority, adaptive design, imputation estimation; census and sampling survey.


**PROFESSIONAL SERVICES** member of ASA since 1976; founding member and permanent member of ICASA. 

**ICASA ACTIVITIES** Member of Executive Committee and Treasurer, ICASA 2005 Applied Statistical Symposium.

**Liu, W.K.**

**PRESENT POSITION** Chair Professor, Department of Statistics & Actuarial Science, University of Hong Kong, 2000; University of Hong Kong. 

**FORMER POSITIONS** Head, Department of Statistics, University of Hong Kong, 1997-1999 inclusive; Professor (Reader), 1995-2000; Senior Lecturer, 1991-1995; Lecturer, 1983-1990; University of Hong Kong Lecturer, 1981-1983, National University of Singapore. 

**DEGREES** Ph.D., 1981, University of Western Ontario; M.A., 1976, York U. (Canada); B.Sc., 1975, York U. (Canada). 


**FIELDS OF MAJOR STATISTICAL ACTIVITIES** Time Series Analysis. 


**ICASA OFFICES & ACTIVITIES** Program Committee (2002-2007); Chairman, Organizing Committee of the 5th ICASA International Conference, Hong Kong, (Aug., 2001). 


**ASSOCIATE EDITORSHIP** Statistica Sinica; Applied Stochastic Models in Business and Industry.

**Lou, W.Y. Wendy**

**PRESENT POSITION** Canada Research Chair in Statistics, Department of Health Care; Associate Professor, Department of Public Health Sciences, University of Toronto, Toronto, Canada. 

**FORMER POSITIONS** Assistant and Associate Professor, Department of Biomedical Sciences, Mount Sinai School of Medicine, New York University, New York, NY (1995-2001). 

**DEGREE** Ph.D. in Biostatistics, University of Toronto, Toronto, Canada (1995). 

**FIELDS OF MAJOR ACTUARIAL ACTIVITIES** Inviting Rums and patterns with biomedical applications; measures for continuity of care; joint modeling for longitudinal and survival data; analysis of patterns and repeats in DNA sequences; methods for health care quality monitoring.


**ICASA ACTIVITIES** Member, Local program chair, ICASA Annual Meeting (1994); Speaker, ICASA International Statistical Conferences and Applied Statistics Symposium. 

**RELATED PROFESSIONAL ACTIVITIES** Member, Regional Advisory Board, ENAR (1997-1999); Representative for the University of Toronto to the Statistical Society of Canada (SSC, 2003-2006); Chair, Local Assistance Committee, JSM (2004); Invited Session Organizer and Chair, JSM and SSC Annual Meetings on various research grants, including NIH, AHRQ, NSERC, CIHR; active reviewer/referee for several professional journals and funding agencies.

**Li, Bing**

**PRESENT POSITION** Professor, Department of Statistics, The Pennsylvania State University, State College, PA. 

**FORMER POSITIONS** Assistant and Associate Professor (1992-2003) Department of Statistics, The Pennsylvania State University, State College, PA. 


From the Editors,
Statistica Sinica
Hwai-Chung Ho, Ph.D.
Jane-Ling Wang, Ph.D.

This is the last report from us on behalf of Statistica Sinica, as we are nearing the end of our third and final year of term. Starting August 2005, Dr. Michelle Liow of the Institute of Statistical Science at Academia Sinica and Professor Xiaoli Meng of the Department of Statistics at Harvard University, will step in as the co-editors of Statistica Sinica. We warmly welcome them aboard and thank them in advance for the countless hours they will devote over the next few years. No doubt the journal will continue to grow and refine under their guidance. Please continue to submit your innovative work through the Statistica Sinica editorial website: http://vexus.stat.sinica.edu.tw/sa/author.htm. This online submission system was set up in 2002 and has functioned effectively to streamlining the review process. Looking back to 2004, there were a total of 233 manuscripts submitted to Statistica Sinica. Among the 211 papers with a first round review completed, 17 percent have been accepted already. The summary statistics for review time during our residence (August 2002 till now) are: 120 days for the median time to first review, 50 days for the median time to revision one, and 194 days for the median total review time.

Over the past few years, Statistica Sinica has been running successfully several special issues on emerging research topics. The most recent theme issue of April 2005 on "Bayesian inference, environmental statistics, time series analysis, and their applications" is based on the papers presented at the NBER/NSF Time Series Conference on September 19 and 20, 2003 in honor of Professor George Tiao's retirement. As most of you may know, Professor Tiao is instrumental in the establishment of both ICSA and Statistica Sinica, he is also the founding editor of our journal. This special issue marks the fundamental contributions and impacts he has made in these topics. We want to take this opportunity to congratulate him for his outstanding achievements and to thank him for his leadership and vision. Next in line is the theme issue entitled "Machine Learning and Data Mining" co-edited by Yi-Lin (Univ. of Wisconsin), Xiaotong Shen (Univ. of Minnesota), and Yuan-Chin Chang (Academic Sinica). The review process of this issue has been well underway and should be completed soon. Please stay tuned.

The 2005 Joint Statistics Meetings (JSM) will be held August 7-11 in Minneapolis, Minnesota. We invite you to attend the invited paper session organized by Statistica Sinica entitled "The Statistics of Brain Imaging". In addition to the three speakers: Professor Moe Chang of University of Wisconsin-Madison, Dr. Will Penny of University College London, and Dr. John Aston of Academia Sinica, Professor Keith J. Worsley of McGill University will serve as the discussant. Please join us to learn the advances in this fascinating research area.

Our journal has enjoyed good reputation and rose quickly to a ranking of top 10 in the category of Statistics and Probability journals according to the latest SCI Journal Citation Reports. The total citations of Statistica Sinica in 2005 increased to 657 from 525, and the Impact Factor rose to 1.336 from 0.605. We owe this success to our predecessors, Professor Ker-Chau Li and Dr. Yi-Ching Yao, the unwavering support of all past and current members of the editorial board, and most importantly, members of the ICSA, and authors and readers of Statistica Sinica. We felt very privileged to have the opportunity to serve our community, as it has been a gratifying experience, which we will carry with fond memory.

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Interview with a Distinguished Scholar

A Conversation with Professor Shing-Tung Yau

By: Kao-Tai Tsai, Ph.D. & Zhiliang Ying, Ph.D.

Last November, we had the privilege to visit Professor Yau at his Columbia University office where he was the visiting Ellenberg Chair Professor. For about three hours, we enjoyed one of the most fascinating conversations. The topics ranged from his experience as a graduate student at Berkeley to his subsequent academic appointments at various universities and research institutions around the world. He also talked about his interactions with many of his peers who were among the top mathematicians in the world. To our surprise, in addition to his research papers, he had three volumes of ancient Chinese classic on his desk. As you can see from his writing at the following, the beauty of his Chinese is no less that from any classic Chinese scholars.

Born in Swatow, China, Professor Yau studied mathematics in high school in Hong Kong. He credited his math teacher and his father, an economist, for his lifelong interest in and devotion to the subject. In 1969, he entered college in the newly opened Chinese University of Hong Kong. Despite a 2-hour daily commute and lack of experienced teachers and up-to-date textbooks, he studied hard and excelled. During his sophomore year, he benefited greatly from a Princeton educated math professor. He also met late Professor S.S. Chern of the University of California at Berkeley. Upon Professor Chern's recommendation, he was awarded a graduate fellowship to pursue PhD in mathematics at U.C. Berkeley, after only two years of college. At Berkeley, he immersed himself into the world of mathematics, taking courses virtually from "3 to 5" and spent the rest of his time in the library. At the age of 22, he was awarded PhD, two years after entering Berkeley.

During his long and distinguished career, Professor Yau taught and conducted research at various places, including the Institute for Advanced Study at Princeton, State University of New York at Stony Brook, Stanford University, the University of Texas at Austin, the University of California at San Diego and Harvard University. His researches in mathematics are extremely powerful, deep and wide. When he came to Harvard University in 1997, Arthur Jaffe, Landon T. Clay Professor of Mathematics and Theoretical Science, made this remark: "Yau's versatility makes him a Renaissance mathematician."

In addition to his research, Professor Yau has also been extremely devoted to promote mathematical education and research in China, overcoming great financial and resource difficulties. He has the foresight of great potential in the applications of statistics to the advancement of science and technology in China. He founded the Morningside Center of Mathematics at the Chinese Academy of Science in Beijing, the Institute of Mathematical Sciences at the Chinese University of Hong Kong and the Zhejiang University Center of Mathematical Sciences in Hangzhou. He travels frequently to many parts of China, giving inspirations to new generations of young Chinese mathematicians.

In 1997, Professor Yau received the National Medal of Science, the highest award given to scientists by the U.S. government, and was cited for "profound contributions to mathematics that have had a great impact on fields as diverse as topology, algebraic geometry, general relativity, and string theory. His work insightfully combines two different mathematical approaches and has resulted in the solution of several longstanding and important problems in mathematics."

The National Medal of Science is only one of many honors he received. In 1982, he was awarded the Fields Medal, the highest honor in mathematics. In 1985, he received the MacArthur "genius" award. When he became a MacArthur Fellow, he humbly noted that "basically, I work in geometry; also on nonlinear equations; also a little bit on mathematical physics. These are all related in many ways."

It was truly an inspirational experience for us to have this interview with him. Following are two of his writings about his experience and philosophy of the pursuit of the ultimate knowledge and truth in life.
為學之道
丘成桐

二零零四年十一月十一日
香港科技大學演講

今日很榮幸到科技大學講讀書的心得，我自幼讀書，得到先父教誨，又得到中學、大學和研究儒諸多良師益友的指導，未嘗偏離正道，可說是幸運之至，願與諸位分享個人的看法。

為學的大環境：

一個人的成長就像魚在水中游泳，鳥在空中飛翔，樹在林中長大一樣，受到周遭環境的影響，歷史上未曾出現過一個大科學家在沒有文化的環境裏，能夠創造偉大發明的例子，一個成功的學者需要吸收歷史上積累下來的成果，並且與當代的學者切磋產生共鳴。人生苦短，無論一個人多聰明，多有天份，也不可能將幾千年來學者共同努力得來的成果，全部人類了解並欣然，了解人生，了解人際關係，累積下來的經驗，不是一朝一夕所能能夠完成的，這些經驗通過不同的途徑在當代學者的方向和著作中表現出來，不同文化背景的學者在現代文化的交流下，有深人的文化背景，有機械的學者比較容易吸取多元化的知識，在思想自由的環境裏，這種知識很快就會萌芽，成為創新的工具和能力。

古代希臘汲取了埃及、巴比倫的文明，諸如此類的例子，學者又能重視當前工作的意念，因此孕育了影響西方文化數千年來的哲學和科學，他們在一、兩百年間集中了一群學者，談論天論，求真求美，將當時積聚的知識有系统的整理出來，他們的積極和他們所用的方法影響到以後文藝復興的科學發展，直至今日。

在同一個時期，中國春秋戰國時代百家爭鳴，由於戰亂，向西向南向東北方的結果，夏商周三代的文化與各地的地方文化融合，學者受到各種文化衝擊，拓展出中國民族創作為能的文風，承先啟後的文化是中國民族優良的傳統，孔子就說過：「周 vero 之，儒家手文政」，孔子很重視「存及學，繼絕世」的做法，在中國本土上，文化熔化不斷數千年，可說是全世界無與倫比的。

秦承先後的文風經驗，開始了文的典範模式，漢唐又繼承這個傳統，並得到西歐和印度文化的融合，達到中國極盛時期，宋朝國力雖然貧弱，但在科技上有辉煌的成就，四大發明都是這一段時間的創作，
四、由於濃厚的好奇心驅使，希望尋覓、探求，來了解大自然的結構，尋找宇宙的奧義，偉大的科學家都有這種好奇心。愛因斯坦說他的好奇心比其他人更濃厚些，才寫得更好一點。誰說科學家就是人類因為好奇而產生的，科學家的創興也跟好奇心有關。例如飛機的發明、太空的探險等，數學上很多領域的探索也是科學家濃厚的好奇心而引發的。

五、科學家和文學家為尋找一個美的結構，可能窮畢生的精力。近代的統一論，某些具體結構，數論或幾何上各種組合的命題，都引起熱烈的研究，而追尋純美則是這種研究的主要動力。數學幾何的創舉即為一例。

學者並不是因為一開始學習就想做大學問，往往由以下兩點作為引子而進入做大學問的途徑：

甲、為了國家和社會的需要，例如電話的發明可以服務人類，第二次世界大戰時雷達和各種遙控方法的研究都因為國事的需要而大有進步。美國的 Wiener，von Neumann，英國的 Turing 在當時的工作成為二十世紀應用科學的基礎，就是很好的例子。

乙、很多學者以追求榮譽為主要的動力。諾貝爾獎金確實使很多青年科 學家拼力去做科學研究。這種榮譽不見得單是個人的榮譽，也可以是民族的榮譽。當年華老榮光，全國興奮，影響了兩代人。

大致上來說很少學者能夠很純粹的只有一個學問的動力，往往有很多原因和背景使他們成長，但當傳世不朽之作，必定必包含第一個因素才能夠完成，上達 Turing 和 Wiener 等大師在純學科上有深入的研究才能在應用科學做出不朽的工作。

我們很容易看得出，以名利、權力为主要動力的學習，當目的達到後，再持續下去，不幸的是，大批的中國學生都由此為目標。

學習的方向受到我們立志的影響，得到師友的薰陶後，培養而固執之，始可成大器。

社會文化和師友對學者影響的影響

事實上，社會的影響是對我們最直接的影響。三百年以前，中國士大夫看不起外國學者，以為他們不懂聖賢書，整個民族自傲且不實事求是地去觀察別人的長處。等到兵敗割地後才開始反省，影響到三國運動的全盤西化，這大時代的變遷，在這個時代長大的學者自然不隨波逐流，跟着大方向走。在今日科學研究的領域中，我們亦能夠看到不同文化背景的科學家有不同的氣質和做學問的方法。

例如美國東方學界有很多學者仍然沿著濃厚的清教徒作風，有和中國人所說的簡介之士。有如孔子在在透，有歸穀之嘆：「歸與，歸與，吾與爾之小子狂又。」就是因為魏簡之士有可取的地方。很多清教徒當然為了自己堅定的理念犧牲生活上的舒服，為學問而做學問，自強不息。


鼓勵的學者說比較難難；德國和日本學者則心細謹慎；而美國這一百年的成就是為什麼新舊兼蓄。著重兼蓄。這是自古以來，一個國家推動學問成功最重要的因素，希臘的雅典、德國的柏林、法國的巴黎、英國的倫敦、蘇聯的莫斯科、中國古代的長安、洛陽等，都聚集了大量的人才。孔子出於魯國，到司馬遷時仍實侍「著論以取其異家」，人才的匯聚確可使風度易俗。

在學校裏，往往見到教授之風在領導上所定的方向。每次試問都不成功，最後成功時的哀惋使學生們覺得興奮，也想自己來一點點的經驗，有時也會看到兩個教授持不同的意見互相批評方書學的缺點，學生會受到這種風氣的感染，認識真理的重要性，了解創造的趣味。

我們又可以看到一批青年的學生和教授肆無忌憚的奔走前人未走過的路。當一群有熱情、有能力的人都在做研究的時候，大部分的人都會受到感染而跟着去奮。

除了與當地的學者交往外，我們也可以從閱讀中與古人和遠方的人交心，「吾自疏流人」就是這個意思。學問既然又是累積的，我們需要知道它的源流，瞭解偉大學者的思路和經驗，來幫助自己的進步。

感情的培養：

初學時總有困難，即使他學之亦然：

周作人

好讀書，不求甚解，每有涉文，欣欣然忘食。

這一點很重要；即使有困難，也要自強不息，讀書能夠欣欣然會有成功的一天。常言道，「巧夫工匠巧匠巧匠，笨手笨腳難能難能」。從前居易、司馬遷、李約瑟等人的作品並不寫得那麼理想，但他們的著作旋風的發展，對專業的發展有濃厚的感概。Watson 在他的自傳裏提到他和 Crick 在研究 DNA 的結構時的瘋狂投入，終於完成劃時代的貢獻。值得注意的是愛因斯坦對於引力場所需的幾何結構，Watson 對所需要的 X-ray 的解析理論並非專家，而是將一貫熱情，而探索成功的。

現今居文的著作來描述他的誠實：

黃心銘之之知之，季九死不渝之勇，

於我們找到喜愛的方向時，就不鬆手放棄。

周豫

民生皆有所取，治之妥善為重，

理想信念未變也，重聽之言不入。

我記得從前為了解決一個很重要的問題時，嶄新思維，有如詩說所吟：

思極邊

天邊遠望，遠水長山。如遊古都，未忘情。從夢里有夢遊士，

思極邊

滄海路之遙遠，獨一夕不朽逝。
我們對每個學科需要「求因」、「明變」和「批判」，才能夠將整個學問吸收到自己思想的系統裏面，再通過發問和思考的過程，向前推進，創造新的學說。

教育的學，需要不斷的觀察大自然的現象，從人類積累而來的經驗中尋找天同的定律，加以破綻、歸納和演繹，循環不息，才能成就大學問，真和美是整個過程的最客觀的導師。

發問

我們在學和思維之後，可能發覺以前所走的方向完全錯誤，或是所要做的問題已經給他人完成。在這個時候，如何自處，就如同坐車，或打敗仗或失態，都是一個考驗我們的修養的時候。

學問與氣質的培養

關於氣質，我們先看：

愛不（感情 優雅）

學問音樂，幽雅導引，節奏同調，至於引而不發，巧於指揮，雖在父
足，不能以移子弟。
表面上，做大學問需要天才才能成功，其實並不盡然。
《華嚴論集》

伯牙學琴於成迷，三年而成，至於神化，聞者賞之，未可得也。成迷曰：吾學不會移情也，吾師何方書之。在氣海中，乃覺神融之至，至

從這裏可以看出氣質亦可以培養，吸收多樣的文後，在高雅的環境影響下，氣質可能會有突變。就如在長期的思考後，我們可能有突然而來的靈感一樣。

氣質的培養最好是從小開始。司馬遷的文章氣吞江河，就是因為父親小就讓他「西至空桐，北過涿鹿，東臨於海，南浮於濟」，又送他到齊魯之學，並跟他交好，所以太史公的學問是靠緣的。

學者面臨大問題時，往往有自信心的考驗，孟子說：「我知言，我善養，浩然之氣」，如果學者有這種浩然之氣，又能博覽群書，就容易無所懼怕了。

志向操守與為學的關係：

在一個學者成長的階段裏，假如操守不良，或志向不正，學問就很容易出倫，

美麗
何昔日之芳草兮，今在其朽艾也。
當其有懷故兮，何其然之苦也。

種種
賞能則棲於雲，賞能則棲於誠。

有些學者早熟而工作很好，但得不到賞識而自怨自艾，終至不能繼續。

一個很著名的例子是漢朝的張敞：

王勃
席賢於長沙，非無王業，但乏明時。

窮則伸頑
王者之六，……非漢文之不能用也，生之不能用漢文也。
其後以自傷哭泣，至於絕域，足亦不屈類為也。夫留之一不見用，
則安好於不用也？不如默默以待其變，而自取死之。噫呼！我志在大而
重少，才有餘而熱不足也。

有人學識不足，而要求上位；有人才略過人，竟學自貶，或自傷過，這都是其文化修養未達，胸襟開闊所致。

以天為師：可以來天理，遠違化。
以道為師：可以致良知，知進退。
他們在理论上先将量子力学与相对论结合，提出了量子场论。这种理论为量子力学和相对论之间的桥梁，使得研究量子系统成为可能。量子场论的引入，使得科学家们能够研究介子在不同条件下的行为，包括在极端时空条件下的行为。

为了理解这种现象，科学家们需要将量子场论与相对论的数学表达式结合。这一过程是一个复杂的任务，需要深入理解相对论的本质和量子力学的原理。

在这个过程中，科学家们发现，介子在极端时空条件下的行为与普通情况有着显著的不同。具体来说，介子可能会在某些情况下表现出类似于中微子的性质，这在量子场论的理论框架下是难以解释的。

为了克服这一难题，科学家们开始研究新的理论框架，试图通过这些理论来解释介子在极端时空条件下的行为。这种研究不仅对物理学本身具有深远影响，同时也为理解宇宙的深层次结构提供了新的视角。

总的来说，介子在极端时空条件下的行为是一个复杂的课题，需要科学家们在理论和实验两方面进行深入研究。通过这些研究，我们有望更好地理解量子场论与相对论之间的关系，以及介子在极端条件下的性质。

[1] 他们发现，介子在极端时空条件下的行为与普通情况有着显著的不同。具体来说，介子可能会在某些情况下表现出类似于中微子的性质，这在量子场论的理论框架下是难以解释的。

[2] 为了克服这一难题，科学家们开始研究新的理论框架，试图通过这些理论来解释介子在极端时空条件下的行为。这种研究不仅对物理学本身具有深远影响，同时也为理解宇宙的深层次结构提供了新的视角。

[3] 总的来说，介子在极端时空条件下的行为是一个复杂的课题，需要科学家们在理论和实验两方面进行深入研究。通过这些研究，我们有望更好地理解量子场论与相对论之间的关系，以及介子在极端条件下的性质。
What is the financial econometrics?

This simple question does not have a simple answer. The boundary of such an interdisciplinary area is always fuzzy and any attempt to give a formal definition is unlikely to be successful. Broadly speaking, financial econometrics is to study quantitative problems arising from finance. It uses statistical techniques and economic theory to address a variety of problems from finance. These include building financial models, estimation and inferences of financial models, volatility estimation, risk management, testing financial economics theory, capital asset pricing, derivative pricing, portfolio allocation, risk-adjusted returns, simulating financial systems, hedging strategies, among others.

Technological invention and trade globalization have brought us into a new era of financial markets. Over the last three decades, enormous number of new financial products have been created to meet customers' demands. For example, to reduce the impact of the fluctuations of currency exchange rates on a firm's finance, which makes its profit more predictable and competitive, a multinational corporation may decide to buy the options on the future of foreign exchanges; to reduce the risk of price fluctuations of a commodity (e.g. lumber, corn, soybeans), a farmer may enter into the future contracts of the commodity; to reduce the risk of weather exposures, amusement parks (too hot or too cold reduces the number of visitors) and energy companies may decide to purchase the financial derivatives based on the temperature. An important milestone is that in the year 1973, the world's first options exchange opened in Chicago. At the very same year, Black and Scholes (1973) published their famous paper on option pricing and Merton (1973a) launched general equilibrium model for security pricing, two landmarks for modern asset pricing. Since then, the derivative markets have experienced extraordinary growth. Professionals in finance now routinely use sophisticated statistical techniques and modern computation power in portfolio management, securities regulation, proprietary trading, financial consulting and risk management.

Financial econometrics is an active field of integration of finance, economics, probability, statistics, and applied mathematics. Financial activities generate many new problems, economics provides useful theoretical foundation and guidance, and quantitative methods such as statistics,
probability and applied mathematics are essential tools to solve quantitative problems in finance. To name a few, complex financial products pose new challenges on their valuations and risk management. Sophisticated stochastic models have been introduced to capture the salient features of underlying economic variables and used for security pricing. Statistical tools are employed to identify parameters of stochastic models, to simulate complex financial systems and to test economic theories via empirical financial data.

There are several books on financial econometrics and related areas. Campbell et al. (1997) is an excellent book on a comprehensive overview of financial econometrics. A distinguished feature of the book is that it includes many empirical studies. Gourieroux and Jasiak (2001) give a concise account on financial econometrics, but some prerequisites are needed. Tsay (2002) is an excellent book on the analysis of time series. It emphasizes on the methodological power of time series techniques on the analysis of financial data. A very nice introductory book on finance econometrics is Ruppert (2004), which aims at undergraduates or master level.

I taught a financial econometrics class for the master students in finance at Princeton University. Last semester, I used the aforementioned books and the book by Fan and Yao (2003) as reference books in an attempt to gather the strengths from these books and to give students a comprehensive overview of the field. While the curriculum is expected to be revised from time to time, I listed the topics covered in my class to give readers an overview.

1. Overview of statistical methods
2. Predictability of asset returns
3. Discrete time volatility models
4. Efficient portfolio and CAPM
5. Multifactor pricing models
6. Inter-temporal equilibrium and stochastic discount models
7. Expectation and present value relation
8. Simulation methods for financial derivatives
9. Econometrics of financial derivatives
10. Forecast and management of market risks
11. Multivariate time series in finance

The field of financial econometrics is much wider than what I presented here. However, the above topics give students a sample of taste on the subject.

I am fully aware the challenge to give an overview of a fast growing field in such a limited space. Readers can easily imagine the undue task if you were asked to write an overview of statistics. Instead of covering every aspect of financial econometrics, I just briefly touch a few important topics where statistics plays an important role.

**Econometrics of financial derivatives**

Financial derivatives are mainly introduced to reduce various exposures of market risks. They are also used in speculative trading to increase leverages. They include options on stocks, stock indices, bonds and bond indices, futures on commodities and currencies, and options on the futures and so on. An option gives the right to its holders to buy or sell certain asset at certain price, called strike price, at or before the expiration. An European option is the one that can only be exercised at the expiration date, while an American option can be exercised any time before its expiration. Options on the stock indices such as the standard and poor 500 index are usually European, while options on individual stocks are usually American. See Duffie (2001) and Hull (2003) for a comprehensive account on this subject.

Options are usually used to hedge against certain financial risks, weather conditions, and natural disasters such as catastrophe events. Consider, for example, a company which expects to receive 250 million euros in 3 months from its sales in Europe. The financial officers of the company do not wish to have unpredictable earnings due to the fluctuations of the exchange rates between the US dollars and euros, making the quarterly earning less predictable. One way to reduce the exchange rate risk is to buy the options, or more frequently the futures, on the currency exchange matured in 3 months with different strike prices. Indeed, the company does not have to buy the actual futures on the US dollars, but to buy the options on the futures of the US dollars. The idea is that if the value of the euro drops, the options on the future will rise to offset the loss in the currency exchanges. As one can see, combinations of different financial instruments can yield various payoffs. The aim is to reduce the market risks to a manageable level. In this sense, financial derivatives serve a similar purpose to that in insurance industry. One advantage of the financial derivatives is that is very liquid, trading at a large volume every trading day.

Since the options give right for holders to buy or sell financial assets, they are valuable. The question is how to value them. The celebrated formula of the Black and Scholes (1973) was derived based on what so called "relative pricing". The basic idea is to produce a trading strategy, which dynamically balances the holdings of the underlying asset and riskless bond, such that the portfolio is riskless and has the same payoff as the option. Through tracking the prices of such a dynamic portfolio, we obtain the value of its corresponding options. Under the Black-Scholes
model, the price for option can be explicitly obtained. It depends on the stock price, the risk-free rate of interest, the strike price, the time to maturity, and the volatility of the asset.

The option writers incur substantial risk in selling underlying options without taking any risk hedging measures. Suppose that an option writer sells 100,000 shares of a call option on a stock with strike price $50 matured in 20 weeks. Suppose that the current stock price is $49 and stock volatility is 20% per annum and the riskless interest rate is 5%. According to the Black-Scholes formula, the value of option is $240,000. If the writer sells it for $300,000, it is expected to make $60,000 or 25% of the option’s value in 20 weeks. If the option writer does nothing to manage his risk, i.e., takes a naked position, and if stock price goes up to $70, he will lose $2,000,000 in option, much more than the premium received. If he takes a fully covered position, namely, buys 100,000 shares at $49 right after issuing the option, and if stock goes down to $39, he will lose $1,000,000 in stock. Clearly, some hedging strategy is needed.

Let me briefly introduce a hedging strategy which helps us understand the derivations of the Black-Scholes formula. The delta-hedging is to hold the shares of the underlying asset according to the sensitivity of the option value to the change of underlying stock price, namely the partial derivative, denoted by \( \Delta \), of the option price formula with respect to the stock price. For the aforementioned example, at the 0th week (immediately after issuing the option), according to the Black-Scholes formula, it can be computed that \( \Delta = 0.522 \) and the writer buys 52,200 shares or 52.2% of 100,000 shares of the option issued. Suppose that after the first week of issuance, the price goes down to $48.1, it can similarly be computed that \( \Delta = 0.458 \). The writer needs to hold only 45,800 shares, and hence needs to sell 52,200 - 45,800 = 6,400 shares. This is a very intuitive decision, as the risk of upward price movement relaxes and the option writer needs to reduce the holding of shares to mitigate the downward risks. Rebalance is needed periodically to keep the risk in check. The cost for producing such a kind of riskless strategy can be computed (interest paid or loss on gain in rebalancing stock) and is approximately the same as the value of the option. The length of rebalance in this example is one week, but this can be chosen to optimize the hedging performance. As the interval of rebalance tends to zero, the cost of producing such a riskless strategy is the value of the option. See Hull (2003).

The art of the implementations of the Black-Scholes formula involves a lot of econometrics and statistics. First of all, one needs to estimate the volatility of an asset from a stock. The available data can be huge. In addition to the historical prices of an underlying stock, related stocks also provide the volatility information of the underlying stock. This results in a multivariate time series and picking relevant ones needs both statistics and fundamental and technical analysts. Further to the complication of the problems is that the stock prices are usually not stationary. Thus, one can not use the historical price volatility based on a large time window. Adaptive choice of time horizons requires statistical studies and empirical research. The precision of volatility estimation has direct implications on the value of the option and confidence intervals are needed for the valuation of options. Further, traders need to estimate the sensitivities of the option prices with respect to the changes of stock prices, interest rates, volatilities and the time to maturity (referred respectively to as delta, rho, vega and theta) and so on. They introduce additional statistical problems for investigation.

Options are actively traded every day. Another possibility is to infer the volatility from the traded option price, which is the inverse of the Black-Scholes formula, called implied volatility. The implied volatility is generally less volatile than the historical one based on asset prices. It should be constant, if the Black-Scholes model holds. However, the implied volatility depends on the characteristics of options such as the strike price or ratio of stock price to the strike price, called moneyness and the time to maturity. Statistical techniques have been introduced to estimate the implied volatility function and the option value surface (as a function of moneyness and the time to maturity) and to understand the observed stylized features such as volatility smiles.

The Black-Scholes formula is derived under the assumption that the price dynamic follows the geometric Brownian motion. Various efforts have been made in extending its applicability to, for example, the yields of bond processes and catastrophe linked securities. The geometric Brownian model has also been extended to various other stochastic models, including stochastic volatility, nonparametric models, and jump diffusion models. These give rise to new financial econometrics problems. We will discuss some of these issues in the stochastic modeling section.

The large volume of option trading also enables one to infer the pricing formula directly from the traded options. This is done through the estimation of the state price density, which is the probability density of the value of an asset under the risk-neutral world or equivalent martingale measure. It does not depend on the payoff function. As such, it can be directly used to price financial derivatives with different payoff functions, which are simply the expected payoffs under the state price density (the integration with respect to the state price density). A nice feature of the state price density is that it can be used to evaluate the price of illiquid derivatives, once it is estimated from more liquid ones. Mathematically, the state price density is the second derivative of the price of the call options with respect to the strike price. Hence, the statistical problem becomes to build a regression model for the prices of options as a function of their option characteristics such as stock spot price, strike price, time to maturity, risk free interest rate and

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dividend yields. See Ait-Sahalia and Lo (1998) for further details on semiparametric and nonparametric approaches to this problem.

Asset pricing and CAPM

Asset pricing tries to understand the prices of claims with uncertain payments. Stock holders, for example, are entitled to the dividend payments over the life time of the stock, which are uncertain. The derivative pricing in the last section is based on relative pricing, inferring the derivative value given the prices of some other assets such as the stocks and the risk free bond. We do not ask where the price of other assets came. There is also a huge literature on "absolute pricing", valuating each asset by reference to its exposure to fundamental sources of macroeconomic risk. An excellent book on this topic is Cochrane (2001).

The quantification of the tradeoff between risk and expected return is one of fundamental problems in financial econometrics. While common sense suggests that riskier investments will generally yield higher returns, it is not until the birth of the Capital Asset Pricing Model (CAPM) that economists were able to quantify risk and the reward for bearing it. Markowitz (1959) laid the groundwork for the CAPM and postulated the investor's portfolio selection problem in terms of the expected return and variance of the return. He argued that investors would optimally hold a mean-variance efficient portfolio. Sharpe (1964) and Lintner (1965) developed further the Markowitz's work and showed that market portfolio (e.g. S&P 500 index, as a proxy) is a mean-variance efficient portfolio. As a consequence of this, they showed the following CAPM: The expected excessive return of any asset over a risk free bond is a multiple, called market β, of the excessive return of the market portfolio. The market β measures the risk of the asset relative to the market portfolio. The CAPM quantifies exactly how the expected return depends on the risk of the asset, measured by the market β.

Since its publication, various statistical techniques have been developed to verify the validity of the CAPM in empirical finance. The early evidence was largely positive. Yet, in the late 1970's, some evidence against the CAPM began to appear in the so-called anomalies literature in which firms can be grouped according to their characteristics to form a portfolio that can be more efficient than the market portfolio. While the evidences against the CAPM are still controversial, various extensions of the CAPM have been proposed to better capture the market risks. These include inter-temporal CAPM (Merton, 1973b), multifactor pricing model such as the Arbitrage Pricing Theory (Ross, 1976), and consumptions based CAPM, among others. These models can be more generally represented by the stochastic discount factor model. A different CAPM amounts to choose a different stochastic discount factor (see, e.g., Cochrane, 2001). They form spectacularly beautiful theory on asset pricing.

Testing the validity of various versions of CAPMs attracts a lot attention in empirical finance. Various testing procedures and statistical methods have been proposed and studied. Statistical techniques have also been used to test risk factors that explain the expected returns of assets over a period of time. For example, Fama and French (1993) build a famous three-factor CAPM to explain the expected excessive returns of assets. They test CAPM using the following three factors: the CRSP value-weighted stock index (a proxy of the market portfolio), the difference of returns on a portfolio of low and high market value of equity firms, the difference of returns on a portfolio of high and low book-to-market value firms. Sophisticated statistical models have been introduced to model the behaviors of consumptions and habits and advanced statistical methods have been applied to test the consistency of these models with empirical financial data.

Stochastic modeling and statistical inferences

The valuation of financial derivatives depends largely on the stochastic model assumptions on the price dynamics of underlying assets. A different asset class requires a different class of stochastic models. For example, the geometric Brownian motion, which has a constant rate of expected return and volatility, can not be used to model bond yields, which possess the heteroscedasticity and mean-revision feature. As they rise, the interest rates tend to be more volatile and there is a positive force pulling the rates down when they exceed a mean level, while as the interest rates go down, the volatility tends to be smaller and there is a positive force driving the rates up when they are below the mean reversion level. Managing and modeling the risks such as natural disaster and weather require a very different class of stochastic models. A stochastic model can only capture certain aspect of underlying stochastic dynamics. This is why there are many models being introduced for the price dynamics of various asset classes.

Options prices depend on the underlying parameters of stochastic processes. The question then arises how to efficiently estimate the parameters from a discretely observed stochastic diffusion process. For an overview, see Fan (2003). If the model has been parameterized, then the maximum likelihood method is a natural candidate. However, except for a few specific models, the likelihood function is difficult to derive analytically and hence hard to implement. One possible remedy is to use the generalized method of moments (Hansen, 1982) to derive some estimation equations and some other features such as local time of stochastic processes to derive a different set of equations. Other methods involve using approximate likelihood, resulting from the Euler approximation or higher-order approximations of stochastic processes when the sampling
interval is small. This is more feasible nowadays, thanks to the availability of high frequency data. The biases of an approximated likelihood method can be reduced by using some calibration methods such as the indirect inference by Gourieroux et al. (1993).

Nonparametric models arise naturally in financial modeling. They aim at reducing modeling biases of parametric models and validating their goodness of fit to financial data. Many of such parametric models are simple and convenient ones to facilitate mathematical derivations and statistical inferences. They are not derived from economics theory and can not be expected to fit all financial data. While the asset pricing theory gives nice pricing formulas when the underlying price dynamic is correctly specified, it offers little guidance in choosing or validating a model. Hence, there are genuine needs for flexible stochastic modeling, and nonparametric methods offer a unified and elegant treatment.

Nonparametric approaches have recently been introduced to estimate return, volatility, transition densities and state price densities of stock prices and bond yields. See Fan (2003). They are also useful for examining the extent to which the dynamics of stock prices and bond yields vary over time. They have immediate applications to the valuation of bond price and stock options and management of market risks. They can also be employed to test economic theory such as the CAPM and other stochastic discount models, and answer the questions such as if the geometric Brownian motion fits certain stock indices, whether the Cox-Ingersoll-Ross model fits yields of bonds, and if interest rates dynamics evolve with time. In these testing problems, nonparametric models serve as natural alternative models to the null hypotheses. Furthermore, based on empirical data, one can also fit directly the observed option prices with their associated characteristics and checks if the option prices are consistent with the theoretical pricing formula. They can also be used to testing whether an underlying asset follows a time-homogeneous Markovian process and can even be used as estimation tools for parametric models.

Volatility, portfolio optimization and risk management

Volatility pervades almost every facet of financial econometrics. It is used in pricing financial derivatives, portfolio allocation to control and manage risks, and computation of risk-adjusted returns for comparisons of relative performance of various financial investments (e.g. mutual funds). It measures the risk of a portfolio and is associated with capital requirement in banking regulations. The topic is prominently featured at the heart of the financial econometrics.

There are two popular classes of widely used models for volatility of discretely observed time series. One is the ARCH and GARCH models and their various extensions. For an overview of the subject, see Engle (1995). These models attempt to capture several important stylized features in financial markets. These include volatilities clustering, heavy tail and asymmetric distributions of returns, persistence of autocorrelation in absolute or squared returns, and leverage effect (stock price movement is negatively correlated with the change of volatility). Various statistical procedures, including quasi-maximum likelihood estimator and robust methods, have been introduced to fit the ARCH-GARCH models. Various efforts have been devoted to investigate the property of this class of models and the performance of statistical procedures. Modeling volatility matrices of multivariate time series poses many new statistical problems with new challenges, as the number of parameters grows quickly with the number of the assets. Recent arrival of high frequency data give rise to new interesting statistical problems.

Stochastic volatility models are another important class for capturing the stylized features of volatilities in financial data. The challenge is that the volatility is not directly observable. Instead, it is driven by a different unobservable random process. The problem here is similar to the error-in-variable regression in statistics (see, e.g., Carroll, Ruppert and Stefanski, 1995). There is a large literature on studying the statistical issues and probabilistic aspects of the models. See Shephard (2004) for an overview.

The portfolio allocation can be formed based on the mean and variance consideration in a similar way to the fundamental work of Markowitz (1959), Sharpe (1964) and Lintner (1965). Its basic idea is to maximize the expected returns while controlling the risks. It can be formulated as a constrained optimization problem. The expected returns and volatility play a prominent role in the portfolio allocation, and statistical techniques are widely used for modeling the returns, volatilities as well as the risk management.

Risk management is to identify risk sources, to measure risks and to control and manage risks. There are large efforts in statistical community on defining and forecasting risk measures. They are directly related to the volatilities of asset returns, and have been widely used in security and bank regulations, proprietary trading, and risk managements. Statistical methods have been widely used in such an endeavor. For an overview, see Jorion (2000).

References
Controversial Statistical Issues: Clinical Trials
Special Topic Editor: Sue-Jane Wang, Ph.D.

Optimality and Flexibility in Sample Size Re-Estimation
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Can medical research problems be translated into a statistical framework satisfactorily? This is a question the statisticians might be asked by the clinical colleagues, which perhaps we ought to ask ourselves first. Most of the time, the answer is a “No.” On one hand, it is the complexity of the clinical study designs that makes a positive answer difficult. On the other hand, a rigidly “better” or “optimal” statistical approach, lacking of flexibility, could be unconvincing and unacceptable to the clinical community. For instance, how do we define “better” when there are multiple endpoints? For a survival study, does “better” mean “delay the occurrence of death” or “reduce hazard”? An optimal test under proportional hazards assumption may even lead to misinterpretation when the assumption is not valid. Even when a well-defined primary endpoint exists, how do we determine an optimal design? In this paper, we will discuss the flexibility versus optimality of the adaptive two-stage designs for sample size re-estimation.

Weighted Z-Test
The idea of variance spending (Fisher) has a special application to a two-stage design. In a two-stage design, the test statistic Z can be expressed as a weighted sum of two Z-values, one from the data of each stage, as $Z = \sqrt{w_1}Z_1 + \sqrt{w_2}Z_2$, where $w$ is a constant weight (0 ≤ w ≤ 1). A typical practical weight is w = N2/N1, where N is the sample size for Stage 1 and N is the originally planned total sample size. The sample size for Stage 1, N0, can be chosen after observing Z. There are different rules for the choice for N0, such as:
(a) If the real treatment effect is the same as observed in Stage 1, choose N0, so that the unconditional power would be the same as planned (Cui, Huang, and Wang, 1999).

(b) If the real treatment effect is the same as observed in Stage 1, choose N0, so that the conditional power under the current trend would reach a desired level.
(c) If the real treatment effect is the same as observed in Stage 1, choose N0 so that the sponsor can afford the conditional power under the current trend is reasonable.

When sample size is extended after re-estimation, the weighted Z-test assigns less weight to patients enrolled after the decision of increasing the sample size than to those enrolled before the decision. Note that there are many different choices for N0 and it is difficult to pre-specify how it should be chosen. In fact, there is really no need to specify a rule, because no matter what value N0 takes, the α-level will be preserved if the weighted Z-test is employed for the final analysis. That is, Z0 is standard normal under the null hypothesis, and thus the α-level critical value of Z0 is still zα.

Researchers have shown that, under rule (a) above, there exists a classical group sequential design which is more efficient than the two-stage weighted-Z design (Tsai and Mehra, 2001). However, the weighted Z-test could be applied to different rules in practice. First of all, by pre-specifying rule (a), Z can easily be found out from the choice of N0 by other people. Secondly, the weighted Z-test introduces a convenient way to re-estimate sample size in clinical trials under various rules for choice of N0. It is flexible as the two components are independent to each other and the weights do not depend on the finding in the stage I analysis, although the increased sample size N0 may do. The null hypothesis is rejected if the weighted Z-test Z lies within the original critical region and the type I error rate is exactly at the nominal level α. The weighted Z-test approach is so flexible that the procedure is not mandated to be pre-specified in the protocol, and the type I error rate α will be preserved at the final analysis. This approach provides a great deal of flexibility to the researchers and the sponsor of a study. Also, since the design rule doesn’t need to be fixed in advance, increasing sample size will not...
reveal interims of observed Zr value, therefore, the concerns of data integrity and potential bias can be addressed satisfactorily. Since there are so many different choices for Ntr, it is not clear how to qualify this flexibility of the weighted Z-test approach into the "optimal criteria." Claiming the "superiority" of the classical group sequential approach to the weighted Z-statistic approach by the comparison based on only one specific choice of rule for Ntr is missing the point of "flexibility" that the weight Z-test approach provides to the clinical trial design.

Un-weighted Z-Statistic with Futility Consideration

In the 1960s and 1970s, many NIH sponsored trials were designed without stopping guidelines. The Policy advisory Boards (they are called the Data and Safety Monitoring Boards nowadays) for these studies reviewed data periodically and one of the statistical procedures they used was the evaluation of "conditional power." During the course of a trial, if one can predict the outcome at the end of the study, then one can "curtail" the trial and make the corresponding decision. However, it is difficult to predict the final outcome for certain until the study is almost over. A variation of curtailment is to evaluate the conditional power (CP), or the chance of concluding a positive study if carried out to the end. Stop the study early if CP is very high or very low, and make conclusions accordingly.

Sample size re-estimation based on unblinded interim results may inflate the type I error rate when using the un-weighted Z-test approach. The weighted Z-test, on the other hand, controls the type I error rate and is extremely flexible, although it violates the one-patient-one-vote principle, which is preferred by many researchers. Lan and Trotz (1997) and Chen, DeMets, and Lan (2004) suggested consideration of both extending the trial and stopping the trial early due to futility in an un-weighted Z-test approach. The basic argument looks like this:

- If we extend the study based on some observations and use the un-weighted Z-statistic, then the q-level will be inflated.
- If the study stops early for futility because the conditional power is low, then the q-level will be reduced.

As long as the inflation does not exceed the deflation, the q-level will be maintained. An interim sample size re-estimation procedure is outlined below. Data is analyzed at the information time t, with the nominal type I error rate α and the conditional power (CP) calculated based on the observed treatment effect $\hat{\Delta}$.

1. If CP ≤ $t$ (lower limit), stop and accept the null hypothesis $H_0$.
2. If CP ≥ $t$ (upper limit), continue to $t + 1$. Reject the null hypothesis $H_0$ if CP > $\alpha$.
3. If $t < CP < \alpha$, extend the trial to $t = m + 1$ so that after extension, the conditional power CPm = $\alpha$. Reject the null hypothesis $H_0$ if CPm ≥ $\alpha$.

As reported in Lan and Trotz (1997), for $t = 0.5$, $\alpha = 0.1$, $u = 0.85$ and $\alpha = 0.025$ ($\alpha$ = 1.96), the probability of type I error with this procedure, estimated by simulations with 1 million replications, is $\hat{\alpha} = 0.022$. Since the realized α is less than 0.025, we may reduce the final critical value to something less than 1.96 and have a more "efficient" procedure. However, this approach may cause the following problems. First, the researcher may not like to have a Z-value less than 1.96 and claim significance. A critical value less than 1.96 may not be large enough to convince the medical society for benefit. Second, the interim look of the study may not occur exactly at $t = 0.5$, and the sponsor may choose $t$ different from 0.1, or $u$ different from 0.85. However, further simulation suggested that when $t \leq 0.7$, $u \geq 0.5$ and $t = 0.1$, and use a critical value of 1.96 for the final test, the q-level will be kept under 0.025. As a result, if the sponsor is willing to stop for futility when $t = 0.1$ and the interim look is taken when $t = 0.7$, the q-level will be controlled. There are many ways to extend the study, and the sample size for stage II may be chosen to reach a reasonable conditional power value.

Re-estimation of sample size may reveal "some" information for observed treatment difference. However, this is a problem we have to face in interim data analysis. For a sequential design trial, if the interim analysis does not trigger stopping, the observed treatment difference is not likely to be too large or too small.

Conclusions

If a clinical trial is in such a stable state then flexibility is probably redundant, however, this is rare in clinical development. With many uncertainties during the conduct of a clinical study, an ability to adapt adequately to new situations is often more important than being able to optimize it with an assumed static state. This is because of the assumptions, and particularly the optimality criteria have been chosen for analytical simplicity rather than validity to the real problems. Thus, it is our observation that rationality is better characterized by flexibility than optimality.

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Issues in Breast Cancer Therapy
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Cancer remains as one of the most deadly diseases. Just breast cancer alone, in 2005, there are 216,000 predicted new cases of female breast cancer in the US and 800,000 cases around the world. Approximately 30% of these patients will have metastatic breast cancer and approximately 80% of the breast cancer patients will die in 10 years after diagnosis.

To advance the Cancer Research, in 1997, the NCI's Clinical Trials Program Review Group recommended to revamp the clinical trials system. The primary goal was to accelerate the pace of clinical cancer research and to enable all oncologists in the US to offer patients NCI-sponsored clinical trials and to simplify and standardize procedures to participate. The new features of the system included the standardization of data collection, online data reporting, simplified informed consent, and to establish a centralized institutional review board (CIRB) process. To do this, the Cancer Trials Support Unit was established to implement a uniform system of patient registration and data collection for all trials in the network. The CIRB would share responsibility for protection of research participants between the local IRB and the CRB. The results of review are distributed to the participating local IRBs via a confidential website.

Principles of treatment

Cell growth cycle usually goes through 5 phases, resting cells (G0), RNA and protein synthesis (G1), DNA synthesis (S), RNA and protein synthesis (G2), and Cell division (Mitosis). The biologists have long assumed the growth of the number of cells following the Gompertzian Model in time,

\[ N_t = N_0 \exp[\log(N_0/N_t)\exp(-bt)] \]

The basis of cancer therapy is to use the so-called "Growth and Kill Model" to interrupt the growth cycles.

Anti-cancer drug can roughly be classified as (1) Chemotherapy, which includes alkylators, antibiotics, antimetabolites, topoisomerase inhibitors, mitosis inhibitors, etc., (2) Hormonal therapy, which includes Steroids, anti-estrogens, anti-androgens, LHRH analogs, anti-aromatase agents, and (3) Immunotherapy, which includes interferon, interleukin-2, and vaccines. For breast cancer, the most commonly used agents are tamoxifen, taxanes (paclitaxel and docetaxel), capcitabine, vinorelbine, and gemcitabine.

Just like any treatment, efficacy usually comes with side effects, and cancer therapy is no exception. Oncologists usually concern most about the grade 3 or 4 toxicity, which could have grave effects to cancer patients. The common toxicities: neuropenia, anemia, nausea/vomiting, diarrhea, alopecia,
peripheral neuropathies, mucositis, and arthropathy/myalgia, etc. The causes of side effect is that the anticancer drug most kill fast growing cells such as blood cells progenitors, cells in the digestive tract, reproductive system, or hair follicles. Other tissues in heart and lungs, kidney and bladder, and nerve system can also be affected.

Chemotherapy

A few strategies are commonly used in chemotherapy administration: (1) mono-therapy, even though somewhat effective, it is less popular nowadays given the proliferation of new anti-cancer agents; and due to this reason, the (2) combination chemotherapy has been used more often than mono-therapy. The basis of the combined effect may be better than the single additive effects of the components with certain degree of reduced toxicity since the components are usually deployed with reduced dose than if the components were to be used by themselves. The setting of drug administration could be adjunctive chemotherapy, which is applied when no evidence of cancer is existent (usually after surgery). The goal is to prevent the cancer cell recurrence. On the other hand, palliative therapy could also be administered before the surgery because the tumor maybe too large to operate or is at the location where it is too dangerous for the tumor to be safely removed. This is the so-called neoadjuvant chemotherapy. In addition to these strategies, one can also have the combined modality chemotherapy, which usually combines chemotherapy, radiotherapy, and surgery in order to have higher response rate.

For women with good performance status, one can apply the single agent strategy, and the combination therapy is usually reserved for patients with symptomatic disease requiring a quicker response. However, for patients whose cancer relapsed after adjuvant therapy, the combination chemotherapy such as docetaxel or capcitabine are usually recommended.

Chemotherapy for metastatic breast cancer: Sequential or Concurrent?

When patients have metastatic cancer, combination therapy is usually the preferred choice. One question is to use the therapy sequentially or concurrently. The answer of this question usually depends on the side-effect profiles of various agents and the physicians’ personal preference with no consensus. For example, a survey was conducted among a group of leading oncologists regarding to the treatment of patients more than 50 years old with ER/PR negative, and HER2 negative, the results as shown in the following table is somewhat divisible:

**Clinical Situations** | Combo. | Seq.
--- | --- | ---
Asymptomatic patients with bone metastasis | 23% | 27%
Asymptomatic patients with several small lung metastases | 36% | 39%
Asymptomatic patients with several small hepatic metastases | 38% | 62%
Patients with bone metastases with moderate pain requiring oral narcotics | 50% | 50%
Very symptomatic patients with visceral metastases | 83% | 18%

In addition, there is no consensus either in terms of what combination agents to use for different kinds of disease status as shown in the following table.

**Agent** | **Adjuvant chemotherapy**
--- | ---
AC | No prior AC | 20% | 25% | (2-3y)
Docetaxel | No prior AC | 16% | 64% | 63%
Capcitabine/Docetaxel | No prior AC | 16% | 3% | 6%
Paclitaxel/docetaxel | No prior AC | 16% | 3% | 6%
Capcitabine/Paclitaxel | No prior AC | 27% | 5% | 6%

However, there seems to be a majority agreement that docetaxel and paclitaxel are the preferred choice in the first line and second line of treatments as shown in the following table.

**Agent** | **1st line** | **2nd line** | **3rd line**
--- | --- | --- | ---
Docetaxel | 65% | 60% | 39%
Paclitaxel | 26% | 26% | 18%
Capcitabine | 25% | 33% | 25%
Vemurafenib | 25% | 25% | 20%
Gemcitabine | 5% | 5% | 5%
Docetaxel | 5% | 5% | 5%
Cyclophosphamide | 2% | 2% | 2%
Paclitaxel | 2% | 2% | 2%

Breast Cancer Risk Factors

There are a few well-known key factors of breast cancer such as age, risk increases with age; reproductive risk factors, higher risk if early menarche or late menopause, late pregnancy; LCIS & DCIS also increase the risk of invasive cancer; prior history and family history of breast cancer; genetics and environmental & life style factors.

Based on the Breast Cancer Detection Demonstration Project database, Gail, et al. derived a model to estimate the relative breast cancer risk, assuming a piecewise baseline hazard rates with the case-control method for both invasive and in situ breast cancer, as shown in the following tables:

**NEDRS**

| Age | 0 | 50 | 50+ |
--- | --- | --- | ---
0 | < 50 | 0.2 | 0.2 |
> 50 | 1.69 | 1.72 |

**AGEMEN**

| Age | 12-13 |
--- | ---
> 12 | 1.01 | 1.27 |

**NUMREL**

| Age | 0 | 12-13 |
--- | --- |
> 12 | 0.64 | 0.47 |
> 12 | 0.28 | 0.23 |

The total relative risk of patients with the same age can be estimated by multiplying the proper cells together, i.e., RR (same age) = RR (Table 1) x RR (Table 2) x RR (Table 3)

On the other hand, Costantino, J., et al. based on SEER database estimated age-specific invasive breast cancer rates, including black women, for invasive breast cancer only, and obtained the following model to estimate the relative cancer risk:

**NEDRS**

| Age | 0 | 50 | 50+ |
--- | --- | --- | ---
0 | < 50 | 0.2 | 0.2 |
> 50 | 1.80 | 1.62 |

**AGEMEN**

| Age | 14-15 |
--- | ---
> 14 | 1.07 | 1.07 |

**NUMREL**

| Age | 0 | 14-15 |
--- | --- |
> 14 | 0.64 | 0.47 |
> 14 | 0.28 | 0.23 |

A few studies were conducted for the purpose of chemoprevention of cancer using Tamoxifen based on the findings of these statistical models. These include (1) NSABP: prophylactic tamoxifen vs placebo, which showed the reduced risk of cancer for all age groups; however, (2) Royal Marsden Hospital tamoxifen prevention trial failed to show significant difference; similarly, (3) Italian tamoxifen prevention trial did not show significant difference; on the other hand, (4) IBIS-I prophylactic tamoxifen trial showed reduced cancer risk by 32% (p=0.013) with VTE as serious side effect. Recently, another trial, STAR trial, is trying to compare Tamoxifen with Roxaloxifene of these effects in cancer prevention.

Chemotherapy General settings

As mentioned previously, neoadjuvant therapy is applied prior to operation, and adjuvant therapy is applied when no evidence of cancer is existent to prevent the recurrence. However, there is no consensus, which is more appropriate or more effective in treating cancer patients. In addition, it is not clear whether tumor size reduction translate into more complete response.

New trends in therapy strategies

New strategies of neoadjuvant chemotherapy include dose-intensity chemos, taxanes, and combination regimens. It is still unknown that neoadjuvant therapy can be used as a surrogate to determine individual benefit from systemic therapy. The neoadjuvant setting is also being utilized to evaluate new systemic agents and predictors of tumor response, including DNA microarray analysis such as in Chang, et al. Even though the results are encouraging, it is far from definitive.

Anti-angiogenic therapy, a targeted regimen, has gaining much attention these days as the therapy tries to stop the new blood vessels to supply the tumor cells the needed fuel to grow. Anti-angiogenic therapy has the advantages of having the potential for low toxicity, possible lack of drug resistance, localized response in the vasculature, reliance of many tumour cells on one capillary, and may be effective across a broad range of cancers.

Anti-angiogenic Combined Therapy

This approach has becoming an interesting research topic. The rationale for potential combined agents in the anti-angiogenic drug is the different targets for these agents, lack of cross-resistance patterns, lack of myelosuppression allows administration of full doses of all agents, and the assumption of additive effects in anti-tumor activity.

Summary

Great advances on cancer treatment had been made in recent years. Many challenging issues still exist and new researches are still in great demand to clarify the most effective treatment regimen. However, this may be difficult because of the diversity of cancer patients regarding to their specific background characteristics such as life style and environmental effect. Even though abundance resource was spent on clinical research, however, the newest results were not always effectively communicated to the practicing.
physicians. Continue medical education has the potential to be a useful component in the clinical research continuum. Inform clinicians about available trials and emerging research findings are critical in the real applications of new findings. Statisticians, being analytical and quantitative, have great opportunities to contribute to the design and analyses of studies in addition to the education to physicians. Cooperative effort of all disciplines with clinicians and marketing staff is also essential to enhance treatment success in cancer research.

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At Cross-Purposes: Cross-Over Trials in Theory and Practice
Stephen Senn, Ph.D.

The controversial cross-over

A cross-over trial is one in which subjects are given sequences of treatments with the object of studying differences between individual treatments (or sub-sequences of treatments). (Senn 2002:p3) In patients such trials are only suitable for chronic diseases with limited disease progression and even then only for the sort of treatment whose effects are reversible. For example in asthma, comparing a class of drug with rapidly reversible effects, would be more suitable than steroids, which have a less dramatic but longer lasting and possibly disease-modifying effect. However, where such conditions are present, a considerable gain in efficiency can be achieved by employing a cross-over trial. Furthermore, for the purpose of studying pharmacokinetics (PK) in healthy volunteers, whether for characterising the PK profile, for examining dose-proportionality, or for comparing the bioavailability of different formulations, or checking for food interactions, the cross-over trial is usually the design of choice.(Senn and Ezzet 1999). The same is frequently the case for pharmacodynamic (PD) studies in chronic diseases in phase II. Hence, despite the fact that there are many purposes for which the cross-over trial is not suited, it remains a design with many uses in drug development.

The outstanding potential problem with cross-over trials is generally agreed to be that of carry-over, which has been defined as, ‘...the persistence (whether physically or in terms of effect) of a treatment applied in one period in the subsequent period of treatment.’ (Senn 2002) (p8). If carry-over occurs the risk is that it may lead to a bias in the estimate of the effects of treatments. There is a huge statistical literature on what to do about carry-over. Unfortunately, much of it while mathematically sophisticated is biologically naive and some is statistically incoherent. (Some examples will be given below.) Recommendations from statisticians have generally fallen into two classes: discussion of approaches to testing for carry-over and examinations of designs that will permit efficient unbiased estimation of treatment effects in the presence of carry-over effects.

The perils of pre-testing

The most notorious example of the former approach is the so called two-stage analysis of AB/BA cross-over trials, that is to say trials in which subjects are randomised to receive either treatment A followed by treatment B or treatment B followed by treatment A. This strategy was originally proposed by Grizzle(Grizzle 1965) but also clearly described by Hills and Armitage(Hills and Armitage 1979) in an influential article which has become a citation classic. The idea is to compare the means by sequence of the total responses for both periods for the patients. In a randomised trial, the difference between these two must either reflect chance or some form of period effect (of which carry-over would be an example), since the main effects of both periods and both treatments must be reflected in the total. If the result is significant, it is concluded that carry-over has occurred and in consequence the second period results may be unreliable. Hence inference regarding treatment effects is based on a simple comparison of first period values.

However, as Freeman(Freeman 1989) showed in 1989, the procedure is quite illogical. Although the test of treatment using first period values is unconditionally unbiased, it is not conditionally unbiased for the test of carry-over. In fact, the two-stage procedure is either irrelevant (carry-over is not ‘found’) or the resulting treatment estimate and associated test are highly biased(Senn 1996; Senn 2002)

Modelling madness

There is a considerable literature on the subject of ‘optimal’ design of cross-over trials. Unfortunately most of this is biologically ‘innocent’. It is doubtful whether many of the authors of these papers have actually ever participated in designing real cross-over trials as opposed to proposing schemes on paper. As an instance, consider two papers in Statistics in Medicine (Jones and Van Der Hoek 1996; Russell et al. 2004) that propose how cross-over trials might be adapted by modifying the sequences in the light of emerging information about treatment effects once all the patients have been treated for a given number of periods. This recommendation betrays an elementary ignorance of a basic fact of clinical trials: patients are recruited for clinical trials when they present for treatment, they do not all fall ill simultaneously that patients are recruited sequentially onto clinical trials. Nobody who had ever worked on clinical trials could be ignorant of this most elementary of facts. For example clinical trials the period of recruitment is far longer than the period of follow up. The net result is that for any cross-over trial with three periods (say) for which all patients had completed two periods of treatments, most would have already finished the trial. In a cross-over trial, period does not have the sense of calendar period, it corresponds to order of treatment.

This particular, error, is not, thank goodness, to be found in all papers in optimal design of cross-over trials. However, another is ubiquitous. This is the reliance on a completely unrealistic model for carry-over whereby this lasts for one period and depends only on the preceding and not on the perturbed treatment. This model has been referred to as the simple carry-over model(Senn 1992) and, as was pointed out by the late Joe Fleiss, flies in the face of common-sense regarding the effects of treatment(Fleiss 1966; Fleiss 1989).

What Fleiss(Fleiss 1986; Fleiss 1989) pointed out was that the model for carry-over was implausible. If a treatment has reached steady state there can be no or little carry-over into itself. Therefore to have a model of carry-over where the effect from A into A is the same as from A into B makes no sense. Although these criticisms were taken to heart by some(Senn 1992; Senn and Lambrou 1998; Senn 2002), others were slower to appreciate their force. However, recently there has been some interest in designs that allow that the carry-over from a treatment into itself is likely to be different from that into other treatments(Knott and Stufken 2002).

Unfortunately, this only deals with the letter of Fleiss’s criticism and not its spirit. Fleiss was considering alternatives to the AB/BA design. These would employ more periods but still compare the two treatments. However if we have three treatments, say A, B, and C, there is also no reason why carry-over from A into B should be the same as from A into C. For example A and B might be treatments in the same class and C might have a different mode of action.

Elsewhere, statisticians have employed the simple carry-over model although this contradicts what else they are doing. For example Fletcher et al(Fletcher, Lewis et al. 1990) considered optimal factorial cross-over designs. When considering the direct effects of treatments, they models they used allowed for main effects of factors and their interactions. Since they also allowed a carry-over term that corresponded to each direct effect, they also allowed for the carry-over of an interaction, which might equivalently be regarded as the combination of two carry-over terms. However, because they were using the simple carry-over model they ignored the interaction of carry-over and direct effect, which would be a more important term than one they allowed for. These two models, factorial for direct effects and simple for carry-over form an incoherent pair. A similar point applies to any dose-finding cross-over that does not employ a simple linear dose-response for analysis but uses the simple linear model. The simple carry-over model implies a linear dose-response so that it cannot apply if the dose-response is not linear(Senn 1992; Senn 2002).
A plea for reasonable research

In 1991, the late and much-lamented Lewis Sheiner, a leading figure in PK/PD modelling and an innovator in non-linear mixed effect modelling more generally wrote a scathing article (Sheiner 1991) in which he criticised the influence that statisticians who were having on research and practice in drug development. At the time I thought that this was unfair. Over the years I have been forced to admit that there was more in Lewis's criticisms than I was initially prepared to admit. I am closer now to accept that sometimes I consider the impact that yet another unrealistic 'solution' to the carry-over problem will have on our reputation with our fellow scientists.

So what is the answer to the problem of carry-over? In my opinion there is no perfect solution but there is no solution that does not have serious implications for the basic pharmacology of what is going on. Washout (whether passive or active) has to be the key to the problem and this requires using background knowledge to design trials. If carry-over is to be modelled then it has to be as part of some integrated modelling approach that includes the direct effect of treatment in the same general framework. Such an approach was, in fact, used by Lewis Sheiner and colleagues (Sheiner et al. 1991) that would make it impossible to have incoherence between carry-over and treatment approaches as was the case with factorial and dose-finding approaches described above.

Is this hopeless? No. There are many cases where it is not. Consider trials in bioequivalence in which the concentration time profile of different formulation is compared. By the convention at baseline it is possible to declare (to the standard provided by the limit of detection) that no carry-over has taken place. Amazingly this has not prevented statisticians suggesting that one should test for carry-over anyway. When I and some colleagues wrote an article (Senn, D'Angelo et al. 2004) criticizing this procedure, pointing out that it was either pointless (carry-over was not detected) or harmful (carry-over was falsely detected) and presented the results of two large series of such trials in which the P-values for carry-over displayed all the characteristics of a uniform distribution, it immediately attracted criticism based on an irrelevant retrospective power calculation rather than an analysis of either the data or the logical circumstance!

Am I claiming that all such optimal design research is illegitimate? No. People are free to study what they wish and mathematics, from which statistics borrows some of its characteristics, is a formal game that does not require practical justification. By the same token, however, I do think that the authors of such papers should not seek to pass them off as a practical solution to any other scientist's problems. Drug development is a serious game played for big stakes (whether measured in terms of lives or dollars) and it too, like mathematics, deserves to be taken seriously. Can it be acceptable to pass off research as a practical solution to trial design without bothering to find out that patients are not treated simultaneously in clinical trials?

For those who are interested in making a practical contribution I offer the following advice.

1. Mathematical models are subjective but applied statistical models need a grounding in reality.

2. Do not ask your design or analysis as a solution to the practical problems of the practising scientist until you have some familiarity with his or her field of research.


Reference


Non-inferiority: The Recent 5-year Odyssey

H.M. James Hung, Ph.D.

For the recent five years the statistical literature on non-inferiority has grown tremendously; see the selected references of Hung, Wang and O'Neil (2005) for a few articles cited therein. On the surface the statistical methodology for non-inferiority trials seems to have advanced very much. However, many would agree that the fundamental controversies remain without a significant progress for resolution while unknowingly the literature does shed many important insights into the unsuccessful of each statistical method and would hopefully help clinical scientists see the end of a seemingly infinite tunnel.


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For ease of presentation, let me use alphabetical letter to represent both a treatment group and its expectation of the expected response. Denote by T the effect of the new treatment T relative to the concurrent positive control C. The same discussion as the articulated below can also be pertinent to the treatment effect in terms of ratio, not just difference. From historical data, we have the parameters of the positive control and the placebo, respectively. For the last five years, we have at least learned that the most popular non-inferiority hypothesis that is the new treatment preserves more than 50% of the effect of the selected control in the current patient population under study. The null hypothesis for the so-defined non-inferiority objective is H0: T - C < -0.5(C-P) and thus the relevant non-inferiority margin is 0.5(C-P). This hypothesis is not testable from the data of the current non-inferiority trial where the placebo arm does not exist. Only when C-P = C-P (often referred to as 'constancy assumption'), the estimate of (C-P) in the historical trials can be used to help test this hypothesis. The constancy assumption can only be judged subjectively or by faith; there is no data for even checking whether this assumption is reasonable because the placebo effect P in the current non-inferiority setting is missing. The story should have ended here and we statisticians should have told the world that no non-inferiority trial can be analyzed. The reality is that statisticians are still being consulted, seen as experts and called to rescues.

With a point estimate and a confidence interval for the effect of the control, (C-P), in the past, the major task is to choose a number that is as close as possible to the true one so that the chosen estimate is equal to the margin of which the value is unknown. This is a statistically impossible task. Our clients (mostly medical colleagues) rarely care about the margin but just ask statisticians to define a statistical margin δ. A natural attempt is to find a lower bound for δ. Take the lower limit of the 95% confidence interval of (C-P). Why? 95% of the time, namely, 95% of many many replicates of the existing historical trials. However, two chosen lower limit of the 95% confidence interval from the existing historical trials, what is the probability that the true value of (C-P) falls outside this chosen limit? Unfortunately, the answer is 'Don't know'. Without this, there is no way to determine why the lower limit of 95% confidence interval is a better number than the lower limit of 50% confidence
interval (better in the sense of smaller statistical risk). This leads to the idea of bringing the statistical behavior of the chosen estimate of $\left(C_0, P_0\right)$ into the non-inferiority inference as stipulated by Hung et al. (2005). For example, the type I error probability of falsely assuming the 50% retention can be assessed on the basis of this probability averaged over the distribution of the $\left(C_0, P_0\right)$ estimates. Alternatively, the maximum probability of this error over the distribution can also be considered. This is the concept of unconditional type I error rate discussed in Hung et al. (2003). The unconditional type I error rate is different from the conventional type I error rate that is defined within the non-inferiority trial and calculated as the proportion of making wrong inference out of many replicates of the non-inferiority trial only. The conventional type I error rate is certainly only conditional on the estimated non-inferiority margin, however it is estimated but treated as if it were a fixed known constant. Once the estimated margin is adopted, non-inferiority in the sense of 50% retention can be asserted if a high level (e.g., 95%) confidence interval of $\left(C_0, P_0\right)$ from the non-inferiority trial rules out the margin. This is the well known fixed margin approach. The only type I error probability relevant to this approach is the conditional type I error probability given the estimated margin. The conditional type I error probability calculated by averaging the conditional type I error probability over the distribution of the margin estimated from the historical trials is not relevant from many statisticians’ perspectives.

Another intuitive approach (often referred to as synthesis approach) is to construct a 95% confidence interval for the parameter $\left(\bar{T}C_0 + 0.5SC_0 - P_0\right)$ that is estimated from the 50% retention hypothesis (recall $H_0$: $\bar{T}C_0 + 0.5SC_0$, equivalently, $\bar{T}C_0 + 0.5\left(C_0, P_0\right)$). There are many methods of this kind, such as Holmgren (1995), Hasselblad and Kong (2001), Wang, Hung, and Tsong (2002), Hung et al. (2003), Rothmann et al. (2003), Wang and Hung (2003a, b), Snappin (2004). If the 95% confidence interval is above zero, then one can assert the 50% retention with the type I error probability at most 5%. Had the placebo arm been studied in the non-inferiority trial, the synthesis approach would have been more efficient. Without the placebo arm, one can only estimate $\left(C_0, P_0\right)$ by the historical estimate of $\left(C_0, P_0\right)$, assuming the condition that the null hypothesis holds. Here comes the crux of the issue. The type I error probability referred here with the synthesis approach is unconditional, which is relevant when the placebo arm is present but may not be when the placebo arm is absent from the non-inferiority trial and the statistical inference for point preservation is of across-trial type. The conditional type I error rate associated with this approach can be as large as 50% under some extreme conditions (Lawrence (2005)).

The major difference between the fixed margin approach and the synthesis approach lies in the concept of type I error probability, as aforementioned. Reconciling this difference has thus far not been successful. It is directly need to move the field of non-inferiority clinical trials forward, at least, for the design and inference purposes. Aside from this difference, a practical limitation to the synthesis approach is that it cannot provide a fixed margin for assessment of its clinical importance; see Hung et al. (2003). Both approaches have their own big drawbacks that might be due to the limitation in the framework of non-inferiority statistical inference, which is based on the fundamental assumption that the true non-inferiority margin is a fixed unknown number.

An alternative statistical framework of inference that may be more attractive, at least, conceptually, is built on the concept of averaging. As articulated in Hung (2001), imaging that there are many active control trials in the same patient population using the same active control, averaging all (C-P) and (C-P) will result in a measure that can probably reflect the center of these parameters. And heterogeneity between them can be quantified by the deviations between the parameters and the average over all. In essence, this concept is the foundation of the Bayesian framework (e.g., Simon (1999)). Such an averaging process, in some sense, updates the location of the effect size C-P from past to the future. However, there will unlikely be any future data for C-P and only the data we have for C-P is from the estimates of C-P. While updating the location of C-P, the data remains at the estimates of C-P. The placebo efficacy $\bar{P_0}$ without future data to updating it. If the placebo effect $\bar{P_0}$ in the non-inferiority trials and the treatment effect T-P can range over the entire real line, then the Bayesian inference will lead to the same conclusion as an appropriate synthesis approach will do. Bounding P (or $T-P$) to a finite interval can probably render a substantial gain of insights about the possible position of (T-P) relative to (C-P); however, the task of bounding mostly depends on a faith or belief. This practice is certainly uninteresting, regardless of whether the distributions of these parameters are incorporated in the non-inferiority inference or not.

In brief, the non-inferiority trial methodology seems to have advanced a great deal, but it actually keeps dwelling on the perhaps unsolvable fundamental problem – how to impute the placebo effect. Do we still want to play this dangerous toy – NON-INFERIORITY? The answer is clear but unfortunately irrelevant. The best advice is "Develop a more effective medicine or use an alternative design (e.g., add-on design) to demonstrate the efficacy".

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Reference

Statistical Hypothesis Testing for Multiple Endpoints in Clinical Trials
Mohammad F. Huque, Ph.D.

Introduction
In a clinical trial, investigators test research questions for establishing that the test intervention is safe and effective in a selected sample of patients with the disease under study. For this purpose, investigators use statistical tests to determine the likelihood that the results of the trial in the chosen sample of patients indeed reflect the safety and efficacy of the study population versus chance findings that do not reflect the benefit of the test intervention. Statistical tests, so frequently used in clinical trials, are founded on the principles of hypothesis testing. The purpose of this article is to explicate conceptual aspects and intricacies of this principle in the context of statistical testing of multiple endpoints of a clinical trial. Hopefully this will motivate investigators in better planning of the trial in addressing solutions to the multiplicity problems. This article, as a background,
will first review concepts for hypothesis testing and p-value for a single endpoint, before getting into the topic of multiple endpoint testing.

**Background**

Testing of hypothesis principles are commonly applied in the design and analysis of clinical trials. Most of these trials include multiple endpoints that require special attention at the planning stage. Occasionally, trials do include only a single primary endpoint for an interim claim. It is worthwhile, therefore, to first review the testing of hypothesis concepts in generality. The basic premise of hypothesis testing is that the investigator begins with the hypothesis that is counter to what he expects to find in his clinical experiment. For example, he asserts that the test intervention is not effective in the treatment of diabetes. He then conducts a planned trial for collecting adequate evidence to determine that this hypothesis is unlikely to be true. In superiority trials, the null hypothesis is that the study intervention is not superior to the control. Similarly, in non-inferiority trials the null hypothesis is that the study intervention is inferior to the control by some specified clinical margin of non-inferiority. In both cases, the investigator conducts a clinical trial for claiming that there is sufficient evidence to reject the null hypothesis.

There are two major types of error that clinical investigators consider when designing a clinical trial. Type I error occurs when a test of a null hypothesis gives a false positive result in favor of the claim that the drug is effective when in fact it is not, or in other words, a false positive result. In the language of hypothesis testing, this is the error of rejecting the null hypothesis when in fact the null hypothesis is true. Type II error occurs when a test fails to reject the null hypothesis that the drug is not effective when in fact it is effective, or in other words, a false negative result. In the language of hypothesis testing this is the error of failing to reject the null hypothesis when in fact the null hypothesis is false. Type I error is also called alpha (α) error and the Type II error beta (β) error. Power is related to Type II error. Power is the ability to show the drug is effective when the true state is that the drug is indeed effective in the patient population with the disease under study.

In testing a null hypothesis, a procedure that is commonly applied is that the hypothesis is selected for a given endpoint for the purpose of testing its null hypothesis. This test statistic is a function of observations of the given endpoint and satisfies two conditions: a) the probability distribution of this test statistics under the null hypothesis is known, at least approximately; b) the larger the value of the test statistic the stronger the evidence of departure from the null hypothesis of the type it is required to test. These two conditions then allows calculation of the probability of the test statistic being equal or more extreme than the observed test statistic, on assuming that the null hypothesis is the true state of nature is called the observed p-value, and is taken as a measure of evidence against the null hypothesis if it is small, e.g., less than 0.05. It represents a way of producing a measure of the strength of evidence" against the null hypothesis.

In planning of a trial, Type I error rate (α) is pre-specified as a level of significance for evaluation the observed p-value. The observed p-value is said to give statistically significant evidence against a null hypothesis at level α if it is less than α. However, when multiple hypotheses are tested, setting of α and interpretation of individual observed p-values are complicated.

**Testing for Multiple Endpoints**

Clinical trials invariably include many multiple endpoints. They are often triaged into primary, secondary and exploratory for managing the complexity of the multiplicity burden. Primary endpoints are primary focus of a trial. Their results determine major benefits of the trial's study intervention. Secondary endpoints on the other hand are considered not sufficient for characterizing benefits of the treatment. They are generally tested for statistical significance for extended indication and labeling of the drug. Objectives of the trial are met. Exploratory endpoints are mainly for hypotheses generating purposes.

Multiple hypotheses testing generally arise when there is more than one research question asked or more than one endpoint tested in the trial. In this case, the potential to draw a false positive conclusion, that is, the Type I error rate, may increase as a result of multiple ways to achieve a successful outcome. For example, consider that in a clinical trial two null hypotheses are tested, one for the effect of a new treatment on the endpoint called pain and the other for the effect of the new treatment on the endpoint called symptom. The trial could produce results by chance in multiple ways that either 1) it gives a false misleading signal that the new treatment is beneficial for the pain endpoint, 2) or gives a false misleading signal that the new treatment is beneficial for the symptom endpoint, or 3) gives a false misleading signal suggesting that the new treatment is beneficial for both the pain and symptom endpoints. Thus, there are three errors which we must keep track of when there are two endpoints tested, and when there are more than two endpoints to test, then there are many such combinations of such false misleading errors to account for in testing.

Therefore, in testing for multiple endpoints where Type I errors can occur in multiple ways, a more complicated measure of Type I error rate is required than that defined above for the single null hypothesis testing case. For this purpose, a measure of Type I error is defined as an overall experimental α, often called the familywise (type I) error rate represented by the acronym FWER. There are ways to calculate this Type I error rate for a statistical test procedure that test for multiple endpoints.

**Two Types of FWER Control**

It is essential that in testing for multiple endpoints, FWER be controlled at a level. This makes the multiple endpoint analyses results interpretable. There are two types of control of this measure named in the literature as the weak and strong control of FWER.

- The term weak control of the FWER is used when it controlled only for testing of a global null hypothesis. A global null hypothesis in testing a family of k multiple endpoints, k being greater than one, states that the study intervention is not effective for any of the k multiple endpoints. Thus, a test procedure that controls FWER only weakly gives test results that are generally mean for non-specific claims. It gives results that could be difficult to interpret as the type I error rate could still remain inflated for endpoint specific claims.

- In seeking a result for a specific endpoint when other endpoints are being tested along with it, there are more null hypotheses considered and involved for the specific endpoint of interest than the simple global null hypothesis. For example, in a cardiovascular trial that is testing the effect of an intervention on three endpoints, namely, total mortality, total stroke and total MI (myocardial infarction), there are a total of 4 null hypotheses configurations for the endpoint total mortality. No efficacy for total mortality Cochran-Armitage with the 4 yes/no possibilities for the efficacy of the intervention for stroke and MI, giving a total of 4 null hypotheses configurations for the total mortality, when testing this endpoint along with stroke and MI. Therefore, in this example, for claiming effectiveness of the intervention specifically for the total mortality, FWER control is needed for each of these 4 null hypotheses configurations for the total mortality. A test procedure that controls FWER in this manner is said to control it strongly and is appropriate for testing for endpoint specific claims.

**Solving Multiple Endpoint Problems for Clinical Trials**

A general principle that is helpful in solving multiplicity problems for multiple endpoints is a three step principle. The first step is to pre-specify primary endpoints and carefully define them with any ambiguity. Primary endpoints are to be clinically relevant and necessary for addressing the primary objectives of the trial. The second step is to define a clinical benefit criterion in terms of the primary endpoints. Such a benefit criterion is often called a clinical effectiveness decision rule or a win scenario that defines what sort of results for the primary endpoints collectively will constitute a benefit of the intervention for the patient population under study. Such a win criterion statistically defines the so called alternative hypothesis space, and counter to it defines the null hypothesis space for the trial involving primary endpoints. The third step is to pre-select an appropriate statistical test strategy for establishing a clinical benefit, that is, for rejecting the primary null hypothesis, that will control the FWER adequately and will have sufficient power of the test. Any omission of these basic steps and designing the trial with the attitude 'let the trial results speak for itself' encourages post-hoc selection of primary endpoints, and the statistical analyses methods, and are likely to produce uninterpretable results because of uncontrollable FWER.

A clinical benefit win criterion can vary from simple to complex depending on the intervention and the drug under study. In an Alzheimer trial, a clinical efficacy criterion usually constitutes a win in two endpoints: the ADAS-Cog Subscale endpoint and the endpoint that measures Clinician's Interview Based Impression of Change. In this case, the null hypothesis is a union null hypothesis in which there is a high failure rate of the intervention simultaneously for both endpoints; the alternative is the intersection hypothesis that there is efficacy of the intervention for both endpoints. Therefore, as there is
only one way to win, that is, if both endpoints must show efficacy of the intervention, there is no inflation of the FWER. In this case it is sufficient to test each hypothesis at the same significance level of α (e.g., α = 0.05).

In a congestive heart failure trial there is a clinical benefit, if the efficacy of the study intervention can be established either for all-cause mortality, or ML, or stroke. In this case the null hypothesis is an interaction null hypothesis that asserts that there is no efficacy of the intervention in any of the three endpoints. For testing this it may be sufficient to use a global or a composite endpoint test that controls FWER only weakly. However, following such a test, often clinical interest is to specify the endpoints that contribute to the efficacy, which requires using a method that controls FWER strongly.

In an epilepsy trial a winning criterion for efficacy is to either win on seizure rate or on seizure severity. In this case the null hypothesis is the joint null hypothesis of two null hypotheses: (1) a single null hypothesis that there is no effect of the intervention on the seizure rate, and (2) a union null hypothesis asserting that there is no effect of the intervention simultaneously on both the drop attack rate and seizure severity. These two null hypotheses, i.e., (1) and (2) can be separately tested using PAAS (prospectively alpha allocation scheme). Thus, seizure rate can be tested at a significance level of α = 0.025, and also attack rate and the seizure severity each can be tested at the same significance level of 0.05. This will control FWER strongly at the significance level 0.05.

Concluding Remarks

Multiplicity problems in a clinical trial could be complex, but statistical methods are available to solve them provided the solution to the problem is prospectively planned. Often clinical efficacy criterion in a trial requires that two or more endpoints show effectiveness of the study intervention. This is often troublesome as some as it raises the bar in terms of the sample size requirements for the trial. However, this is a clinical issue related to what constitute a sufficient clinical evidence for assuring that the study intervention is safe and effective for the intended patient population. Some sample size burden can be reduced by considering dependence between endpoints that is common in clinical trials.

It is important that multiplicity problems of a trial be addressed at the protocol planning time. Post-hoc decisions regarding selections and definitions of primary endpoints, the efficacy ‘win’ criterion and statistical analyses methods are problematic in clinical trials. Such decisions are likely to produce un-interpretable results because of FWER control issues.

Disclaimer: Views expressed in this article are those of the author and not necessarily of the U.S. Food and Drug Administration.

References

5. O'Neill, R.T. Secondary endpoints can not be validly analyzed if the primary endpoint does not demonstrate clear statistical significance. Controlled Clinical Trials 1997, 18: 550-556

Mohammad F. Huque
Division Biometrics III, Office of Biostatistics, OpaSS, CDER, FDA
Email: huque@cderr.fda.gov

Commentary on Alpha Allocation Design Strategies in Clinical Trials Using Genomic Signature

Stue-Jane Wang, Ph.D.

Introduction

In conventional randomized clinical trials, investigation of a therapeutic effect requires a clearly stated a priori hypothesis. The hypothesis to demonstrate maybe that the experimental treatment is superior to placebo or that the new treatment is not much worse than an effective active-control drug. When a categorical covariate-adjusted analysis is pre-specified, eligible patients may be randomized by stratifying on the categorical covariate, e.g., moderate vs. severe disease status at baseline. Alternatively, simple two-arm randomization can be conducted. The treatment-by-covariate interaction may be explored, particularly, when there is suspicion that the treatment effect may differ between strata.

With the availability of genomic high throughput technology, it is foreseeable that the hypothesis testing characteristics of Phase III trials will remain. However, to make appropriate statistical inference, what is likely to adopt is the selection of patients to be included in a Phase III trial. To the drug developer, the goal is to identify the right patient population that demonstrates the therapeutic effect. In contrast, the patients will seek the drug that is right for them (sometimes called individualized medicine).

The use of genomics to identify the therapeutic effect hinges on an appropriate identification of a genomic composite biomarker (GCB). The GCB is a genomic signature or classifier that consists of a set of genes and its information is described by a pre-specified prediction algorithm with a pre-specified cutoff threshold, known as a prediction score or risk score. A commonly known prediction score is a weighted average of the genomic effect pre-selected from the genome-wide scanning or candidate genes, e.g., for a dichotomous GCB classifier, a patient is classified as GCB+ if his/her risk score is beyond the pre-selected threshold, and GCB-, otherwise.

The clinical/statistical hypothesis of interest is whether the purported treatment effect is derived from the conventionally defined patient population or the molecularly targeted patient population. Recently, Simon presented a simple and conservative alpha allocation method, viz., by splitting the usual 2-sided alpha of 0.05 to 0.04 for the conventionally defined patient population and 0.01 for the molecularly targeted patient population. Incorporation of the correlation between the two types of patients studied would allow a less conservative alpha allocation, as the correlation is a function of the sizes for the all-comer and GCB-present patients (Wang, 2005). For instance, if the estimated prevalence of GCB+ is 50% and a 2-sided 0.04 alpha is allocated for the all-comer hypothesis, an alpha level of 0.0164, instead of 0.01, would satisfy the requirement of an overall 5% alpha error control. The 0.0164 becomes 0.036 if 90% of the all-comers are GCB+.

Statistically, one can use the closed test strategy by testing the all-comer hypothesis and the GCB-present hypothesis individually at 0.05 level, but, only after the global null hypothesis of the above two hypotheses is rejected at the 2-sided 5% level. The pre-requisite of these three general approaches is that the GCB classifier needs to be identified and clinically validated from trials other than this prospectively planned and conducted trial. There may be resistance with use of the closed test procedure in that, if at all, the therapeutic effect in the molecularly targeted subgroup should be much more profound than the unselected patient population, thus, requiring possibly a smaller alpha allocation than the 5% level to avoid chance finding. A counter argument is that the global hypothesis serves as the gatekeeper before initiation of the GCB+ component hypotheses.

Tarceva (erlotinib) Table 5 is recently approved for its prolonging survival by two months on average as compared to placebo. The estimated hazard ratio and its 95% confidence interval were 0.73 (0.61 to 0.86), p=0.001. Tarceva is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. A post-hoc interest, following the approval of Iressa (gefitinib), in 2003, was on the EGFR+ or EGFR− subgroup studied. The EGFR expression status was ascertained for approximately 1/3 of the patients who already had tissue samples prior to study enrollment. It turned out that the point estimates and the 95% confidence interval of the hazard ratio on all cause mortality from the univariate exploratory analyses were 1.01 (0.65 to 1.57) in EGFR+− subgroup, 0.65 (0.43 to 0.97) in EGFR+ + subgroup and 0.76 (0.61 to 0.91) in the EGFR− subgroup.
Regional Activities

Hong-Kong
Haailing Yang, Ph.D.

International Conference on Statistics in Honour of Professor Kai-Tai Fang's 65th Birthday (Fang65) June 20–24, 2005, Hong Kong:

This conference will be held from June 20-24, 2005 at Hong Kong Baptist University. The conference is held in honour of Professor Kai-Tai Fang's 65th birthday. Professor Fang, Fellow of the American Statistical Association and the Institute of Mathematical Statistics, is the co-inventor of the uniform experimental design. He has made a lot important contributions on many aspects of statistics. The Conference featured many leading experts and distinguished speakers, plenary speakers include 15 well known statisticians. The scientific committee chairman are Jianying Fan (Princeton University) and Fred J. Hickernell (Hong Kong Baptist University) and the local organizing committee chairman is Sung Nok Chiu (Hong Kong Baptist University. For more details, please go to the conference's website. The website address is http://www.math.hkbu.edu.hk/Fang65/.

The 5th IASC Asian Conference on Statistical Computing (Iasc Asian05) 15-17 December 2005, Hong Kong

The conference is organized by the International Association for Statistical Computing (IASC), Asian Regional section and co-organized by the Hong Kong Statistical Society and the Department of Statistics and Actuarial Science, The University of Hong Kong. The Keynote speakers are Professors Peter Hall (Australia National University) and Tze-Leung Lai (Stanford University). The conference chair is W.K. Fung (The University of Hong Kong), co-chairs are Y. Tanaka (Nanzan University) and J. C. Lee (Korea University). The organizing committee chair is K.C. Yuen (The University of Hong Kong) and the Scientific Programme Committee chair is P.L.H. Yu (The University of Hong Kong). For details please go to the conference website at: http://www.hku.hk/statistics/IASCAsian05/.

The 2005 Hong Kong Statistical Conference, Hong Kong Statistical Society, 17 December 2005

Hong Kong Statistical Society will hold a conference on 17 December 2005. The organizing committee chair is W.K. Fung (The University of Hong Kong) and the scientific committee chair is M.S.S. Lee (The University of Hong Kong). The keynote speaker is T. L. Lai (Stanford University). For more details, please visit the conference website at: www.hku.hk/statistics/HKSS2005.

Conference on Probability with Applications to Finance and Insurance: A joint HKU-HKUST-CUHK-Fudan meeting celebrating Professor Tze Leung Lai's Sixtieth Birthday, December 19-21, 2005, The University of Hong Kong

The conference is for Prof. Lai's sixtieth birthday. Professor Tze Leung Lai, Chairman of the Department of Statistics, Stanford University, USA, is a world-renowned statistician. He won the John Simon Guggenheim Fellowship at Berkeley and the prestigious COPSS Award (Committee of Presidents of Statistical Societies Award) in 1983, and was Higgins Professor of Mathematical Statistics at Columbia University, USA, before joining Stanford. He is a Fellow of the Institute of Mathematical Statistics and the American Statistical Association, and is a member of the Steering Committee for the Interdisciplinary Program in Financial Mathematics at Stanford. 24 leading experts on probability theory, mathematical finance and actuarial science will give talks during the conference.
Workshop on Embedded Options in Insurance Products, February 19, 2005, The University of Hong Kong

A half day workshop on embedded options in insurance products was held on February 19, 2005. Prof. W.K. Li (The University of Hong Kong) gave an opening address, and Professors H. U. Gerber (University of Lausanne), M. J. Goovaerts (Catholic University of Leuven), Y.K. Kwok (Hong Kong University of Science and Technology) and X.S. Lin (University of Toronto) are the speakers. For more details, please visit the workshop website at: http://www.hku.hk/statistics/workshop/

Hailiang Yang, Ph.D. is Associate Professor of the Statistics and Actuarial Science Department, The University of Hong Kong.
Email: hlyang@hkusua.hku.hk

Taiwan
C. Andy Tsao, Ph.D.

Recent Statistical Conferences and Workshops in Taiwan


2005 Statistics Camp for Undergrads

2005 Taipei Symposium on Medical Statistics
June 18, National Taiwan University, Taipei.
URL: http://ccms.ntu.edu.tw/~epidem/biostat/TSMS/

Statistics and Machine Learning Conference 2006 in Taiwan
URL: http://www3.stat.sinica.edu.tw/ML/index.htm

C. Andy Tsao, Ph.D. is an Associate Professor of Statistics, Department of Applied Math at National Dong Hwa University, Taiwan.
Email: chtsao@mail.nduu.edu.tw.

A scenery of Hong Kong

An old gate in ancient Tainan City, Taiwan

ICSA 2006 APPLIED STATISTICS SYMPOSIUM

June 14-17, 2006, University of Connecticut, Storrs, Connecticut, USA

The 15th annual ICSA Applied Statistics Symposium will be held at the University of Connecticut’s main campus in Storrs, Connecticut, USA. Meeting participants will enjoy the peaceful beauty of this rolling-hills campus setting with all the advantages of New England’s top ranked public university. As the host site of the 2006 ICSA Symposium, the University is proud to showcase the results of “UCONN 2000”, an unprecedented 10-year, $1 billion renovation and construction program to rebuild, renew, and enhance the University of Connecticut and its facilities. The Storrs campus is located in the northeast “Quiet Corner” of Connecticut near the metropolitan areas of Hartford, Boston, Springfield, Providence, and New York City. Within a half an hour of the Quiet Corner, you will find attractions such as Hartford, Providence, Old Sturbridge Village, Foxwoods Casino, Mashantucket Pequot Museum & Research Center, Mohegan Sun Resort, and Mystic Seaport. Newport and Boston are approximately an hour and a half away and New York City is less than three hours.

Organized by the International Chinese Statistical Association, this annual statistics symposium will feature three keynote talks by Professors James O. Berger of Duke University and SAMSI, Xiao-Li Meng of Harvard University, and Terrence P. Speed of the University of California at Berkeley and the Walter and Eliza Hall Institute of Medical Research in Australia. Plenary talks will be given by Professors Kung-Yee Liang of the National Health Research Institutes, Taiwan, R. O. C. and Johns Hopkins University and Jun S. Liu of Harvard University. There are also one-day short courses, invited and contributed talks, and a poster session. The program committee

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invites talks on all aspects of statistics. Abstracts are due April 15, 2006. Please contact Hongyu Zhao, Yale University, email: hongyu.zhao@yale.edu, for further information. In addition, the symposium sponsors ICSA student awards and a travel fellowship. The deadline for applying for the awards is April 1, 2006. For further questions, please contact Professor Heping Zhang, Yale University, email: heping.zhang@yale.edu and Fred C. Djang, Bristol-Myers Squibb, email: djangf1@bms.com.

Short courses will be scheduled on Wednesday, June 14, 2006 and technical sessions will start on Thursday, June 15 and end Saturday, June 17, 2006. All conference participants will be cordially invited to attend a Reception / Mixer on Wednesday (June 14) evening during which a cash bar and complimentary hors d'oeuvres will be available. Thursday evening is Casino Night. All participants will be invited to visit Mohegan Sun Casino and for their convenience, charter buses will be provided to the casino. The conference banquet will be on Friday evening.

All keynote and plenary sessions will be held in a newly built multimedia room that is air-conditioned with full audiovisual capabilities. The rooms for the parallel sessions are equipped with screens and LCD projectors. The Mixer and banquet will be held in the UCONN Rome Commons Ballroom.

There are two choices of on-campus lodging: hotel accommodations at the Nathan Hale Inn & Conference Center (www.nathanhaileen.com) and residential accommodations at the South Campus Residence Hall. For the hotel, rooms are available on a first-come first-serve basis at a special group rate of $95.00 + tax if reservations are made no later than May 13, 2006. At the South Campus Residence Hall, rooms are air-conditioned, suite style with two bedrooms, a common living space, and a shared bathroom. Each bedroom has 2 single beds. Linens and local phone service are provided. For both the hotel and the residence hall, there is the option of single or double occupancy. Please note that if the hotel becomes full, there will still be availability at the residential complex. Please visit www.icsa.org for more information. Shuttle transportation will be provided to and from Bradley International Airport and the Hartford train station.

The 15th ICSA organizing committee welcomes you to attend the symposium. For technical information about registration, transportation, or conference logistics, please contact Professor Ming-Hui Chen, Statistics Department, University of Connecticut (mhchen@stat.uconn.edu).

Executive Committee: Greg Wei (chair), greg.cg.wei@pfizer.com, (860) 732-1284, Ming-Hui Chen, Fred C. Djang, Heiping Zhang, and Hongyu Zhao.

Local Organizing Committee: Ming-Hui Chen (chair), mhchen@stat.uconn.edu, (860) 486-6984, Fred C. Djang, Lynn Kuo, Eliaha Gaoi, Naisee Ting, Yazhen Wang, Greg Wei, Heiping Zhang, Hongyu Zhao, and Bob Seguin of University Conference Services, U. of Connecticut.

Treasurer and Registrar: Lynn Kuo, lyu@stat.uconn.edu, (860) 486-2951.

Assistant Treasurer and Registrar: Fang Yu, fangyu@stat.uconn.edu, (860) 486-5804

Program Committee: Hongyu Zhao (chair), hongyu.zhao@yale.edu, (203) 785-6271, Mingxiu Hu, Gordon Lan, Jane Liang, Jun Liu, Yazhen Wang, Greg Wei, and Zhiliang Ying.

Contributed and Poster Papers: Jane Liang, jane.g.liang@pfizer.com, (860) 732-0775.

Short Course Committee: Yazhen Wang (chair), yzwang@stat.uconn.edu, (860) 486-3415, Ming-Hui Chen, and Greg Wei.

Fund Raising Committee: Naisee Ting (chair), naisee.ting@pfizer.com, (860) 732-4871, Fred C. Djang, Lynn Kuo, Ts-Hsin Li, Greg Wei, and Eric Yan.

Student Award Committee: Heiping Zhang (chair), heping.zhang@yale.edu, (203) 785-6272, William Pan, and Hongyu Zhu.

J. P. Hsu Memorial Scholarship: Fred C. Djang (chair), djangf1@bms.com, (203) 677-7247, Tai-Tsang Chen, and Naisee Ting.

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Please Make Check Payable to: I.C.S.A. Mail This Form & Fees to: ICSA c/o Ivan S. F. Chan, 6 Sarah Court, Dresher, PA 19025

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**International Chinese Statistical Association**

**Membership Application & Renewal Form**

**International Chinese Statistical Association**

**Membership Application & Renewal Form**

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Calendar of Meetings

Dec. 12-14, 2005 – Dr. C.Z. Wei Memorial Conference
Location: Academia Sinica, Taipei, Taiwan.

Dr. Ching-Zong Wei, the former Director of the Institute of Statistical Science, Academia Sinica, passed away last November at age of 56 after a long struggle of brain tumors. To honor his memory, a three-day conference sponsored by the Institute will be held on December 12 to 14, 2005 at Academia Sinica, Taipei, Taiwan. Many of Ching-Zong’s friends and colleagues all over the world will attend the conference. Following is a partial list of committed speakers: Rajendra J. Bhansali, Ngai Hang Chan, Louis Chen, Rainer Dahlhaus, Richard A. Davis, David F. Findley, Lei Guo, Chen Hisiao, Chao A. Hsiung, In-Chi Hsu, Genshiro Kitagawa, Tze Leung Lai, Wai-Keeung Li, Bent Nielsen, Bennet M. Pötscher, Jorma Rissanen, George Tiao, Ruey S. Tsay, Chien-Fu Jeff Wu, Zhiheng Ying, Chun-Hui Zhang. For more information about the conference, please contact Hwai-Chung Ho (hcho@stat.sinica.edu.tw) or Ching-Kang Ing (cking@stat.sinica.edu.tw)

Members News

Dr. Zeny Feng, a member of the ICSA, is the recipient of the prestigious Pierre Robillard Award for the best Ph.D. thesis defended in Canada in the year of 2004. She has been under joint supervision of Professors Mary Thompson and Jiahua Chen in the Department of Statistics and Actuarial Science, University of Waterloo. The title of her thesis is “Statistical methods in affected sib pairs analysis”.

Professor Jiahua Chen, the current president of the ICSA, is the recipient of the CRM-SSC award. This prestigious award, jointly sponsored by the Statistical Society of Canada (SSC) and the Centre de recherches mathématiques de Montréal (CRM), is given each year to a Canadian statistician in recognition of outstanding contributions to the discipline during the recipient’s first 15 years after earning a doctorate. Professor Jiahua Chen earned his Ph.D. in 1990 under the supervision of Professor Chien-Fu Jeff Wu from the University of Wisconsin-Madison. He is the second student of Professor Wu in a row to win this award.

Our Sincere Thanks!
The Editorial Team

Just like the previous two and half years, many good friends have taken time from their busy schedules to write for this issue of the Bulletin. Without their help, this issue of the Bulletin would be impossible.

We especially appreciate the generosity of Professor Yau to take time for us to conduct the interview. We had one of the most intriguing time in our life. The conversation of his experience in Hong Kong, Berkeley, and other parts of the world, as well as his learning process and his ambition to build up the mathematical research in China made it the most unforgettable afternoon in our memory.

We would also like to thank Professor Fan of Princeton University of his article about financial econometrics. This is both a highly interesting and challenging area of research. In addition, lots of the statistical methodologies can find its applications in this fascinating field.

We would also like to express our thanks toward Dr. Yang of Hong Kong and Professor Tsao of Taiwan for their continuing effort to provide us with the local statistical activities in their respective regions. These efforts had greatly enhanced the interactions between the statisticians around the world.

The authors of the contemporary statistical issues also deserve our special thanks. The topics discussed there continue to be one of our highlights in the Bulletin due to its real world applications and the medical relevance.

We wish that we can mention all the names of the contributors in the past three years. Even though we can not really do that, we would like to offer our most sincere thanks toward all the wonderful friends around the world for making our life so much more enriched and memorable.

Dinner Cruise at JSM – Feel the History and Share the Romance

This year’s ICSA dinner event at JSM will be more than a dinner. It will be a dinner cruise on the beautiful Mississippi River! The historically narrated excursion will leave downtown St. Paul around 7:15 pm on August 10th. The buses will board the passengers right after the annual ICSA meeting at 6:30 pm on 8/10 at the entrance of the conference center. The tickets will be sold at ICSA booth during the conference. We are exploring the possibility to take early reservations before the conference starts. If offered, the details will be posted on the ICSA website.

Ticket price information: before noon of Aug. 9th: $40 (adult), $30 (student, below cost!), and $20 (child); after noon of Aug. 9th: $45 (no discount to students or children). You can find more information on the cruise at the riverboat company’s website: http://www.riverrides.com/. It was said that Saint Paul and Minneapolis exist today because of riverboats. You don’t want to miss the opportunity to feel the history of Minnesota on the cruise.

We have set up a local organization committee consisting of the following members: William Li (Chair), Wei Pan, Tiefeng Jiang, Na Li, Baolin Wu. The committee welcome you to Minnesota and look forward to seeing you on the cruise. Please contact William Li at wli@csom.umn.edu for any questions.

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