International Chinese Statistical Association

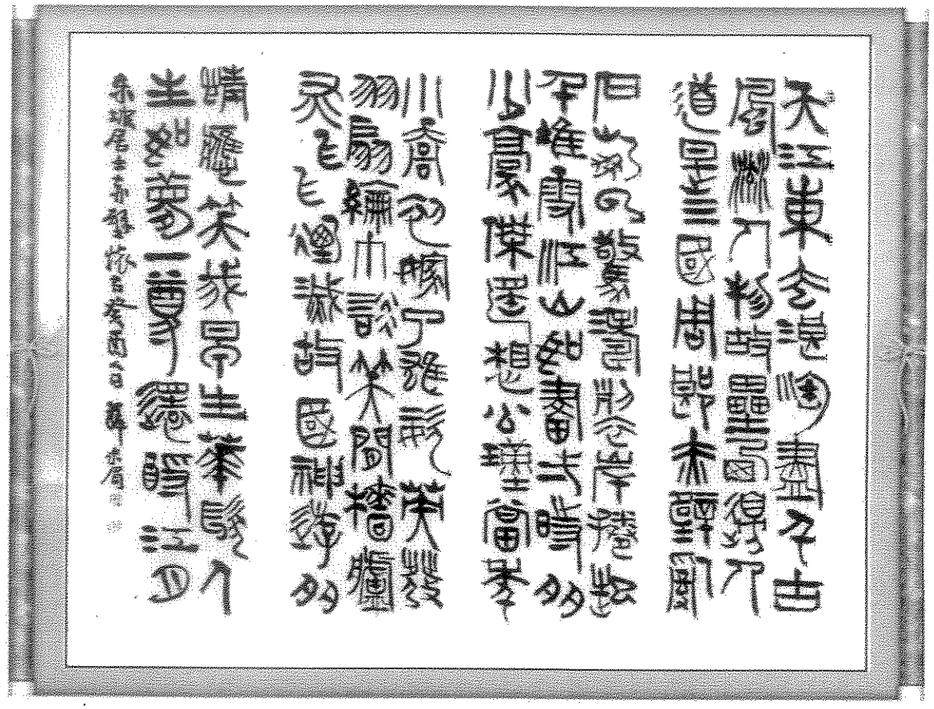
http://www.icsa.org

泛華統計協會

Features:

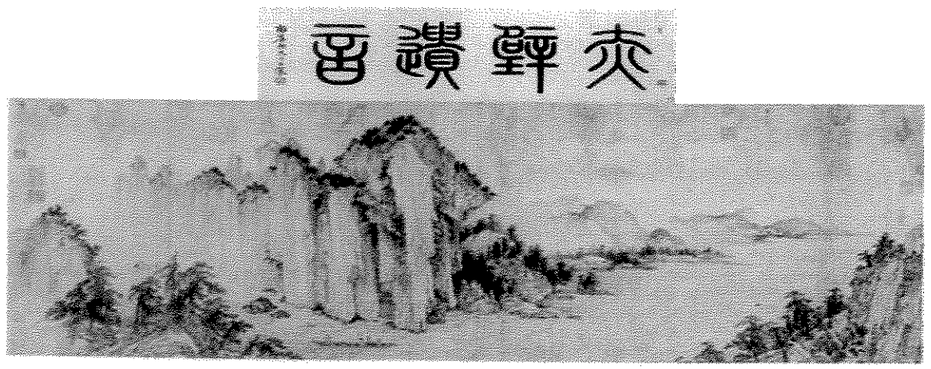
- Interview with a Distinguished Mathematician
- Candidates of ICSA Officers
- Special Feature Article: Financial Econometrics
- Controversial Statistical Issues
- Meeting Announcements
- Highlights of 2005 Applied Statistics Symposium

Bulletin July 2005



Chinese Calligraphy

Calligraphy is one of the four arts in ancient China to symbolize the classic scholarship. There are varieties of styles in Chinese calligraphy. For example, the words above and the words inside the back cover have exactly the same contents by a famous scholar in Sung dynasty even though they look very much different.



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.

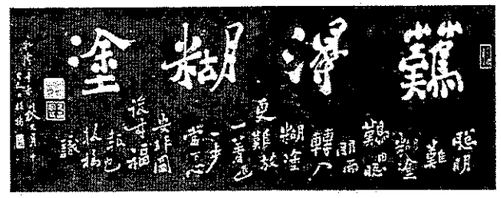
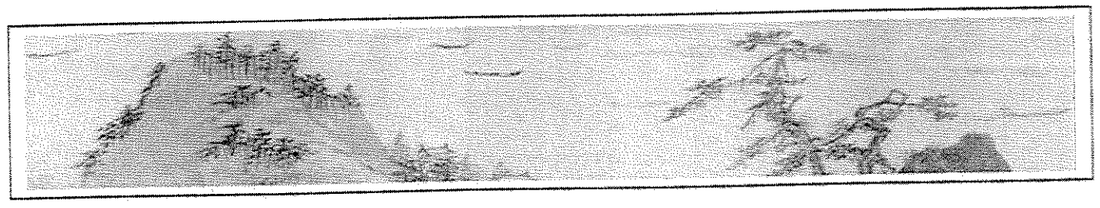


Table of Contents
ICSA Bulletin, July 2005

Editorial Members
ICSA Bulletin, July 2005



Committee Chairs
ICSA, 2005

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Jiqian Fang	Wayne Weng
Xumin He	Greg Wei
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Program Committee
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Weiying Yuan
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Strategic Committee
Frank Shen

Submission Guidelines
ICSA Bulletin

Articles
The ICSA Bulletin 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 papers. If submitted in papers, 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 ICSA Bulletin welcomes the submission of advertisements related to the profession of Statistics. The fee for the 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 tsai0123@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 this writing, 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.

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 wanted 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* (JBES) at no additional cost!

- ICSA members **residing in all other counties** may join the ASA as a full member for only $75 (U.S.) per year, a $10 savings off of 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 statistics 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) 231-3473 or emailing asainfo@amstat.org. We look forward to welcoming you into the American Statistical Association.

Sincerely, ICSA President & ASA President

INTERNATIONAL CHINESE STATISTICAL ASSOCIATION YEAR 2005 APPLIED STATISTICS SYMPOSIUM

泛華統計協會

Yes, as an ICSA member, I would like to join the American Statistical Association (ASA)*:

☐ **As a new member at the economically developing country rate of $35 (U.S.).**
I reside in _____ (name of economically developing country)

☐ **As a new member at the full member rate of $75 (U.S.).** $10 off the regular full membership rate.

***This offer is only valid for new ASA memberships.**

CONTACT INFORMATION:

NAME:_____

COMPANY (IF APPLICABLE):_____

ADDRESS:_____

CITY/ STATE/ ZIP:_____

COUNTRY: _____

PHONE/ FAX/ EMAIL:_____

PAYMENT INFORMATION:

Please check one:

☐ CHECK/MONEY ORDER ☐ AMERICAN EXPRESS ☐MASTERCARD ☐VISA

NAME ON CARD:_____

CARD NUMBER:_____

CVS # (3-digit security number located on the back of your card):_____

EXPIRATION DATE (Month/Year):_____

SIGNATURE OF CARDHOLDER:_____

PLEASE SEND THIS FORM TO:

AMERICAN STATISTICAL ASSOCIATION
1429 DUKE STREET
ALEXANDRIA, VA 22314 USA
OR
FAX TO (703) 684-2037

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.

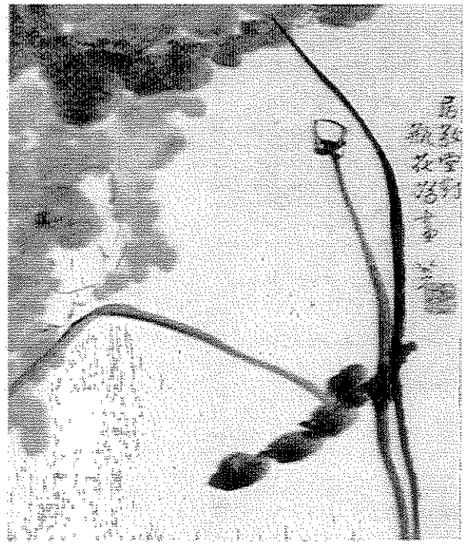
This year we will elect several officers, including 2006 President-Elect, 2006 Biometrics Section Chair, and 6 Directors of the ICSA Board (2006-2008 term). I would like to thank the Nomination Committee, under the leadership of Xuming He, in selecting a list of very strong candidates. By now you would have already received the ballot (if not, please check the web site 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 Sinica 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 forgot 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: J.Zhao@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



Reports From Committee Chairs

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 10th. 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 ICSA 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@groton.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 helps 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 change of Jiann-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 Marriot Hotel and Conference Center at College Park, Maryland. But when we noticed that a new Marriot 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.

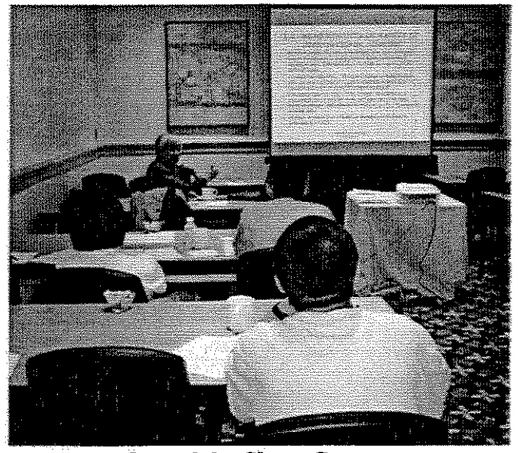
By the end of 2004, the program seemed to be in great shape but the worry of funding grew. One thing we learned about symposium spending is that there is no unbiased estimate of hotel and conference expense. There is only under-estimate. Hence, we recruited Jun Zhao to help out with corporate fund raising. 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 "ICSA 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

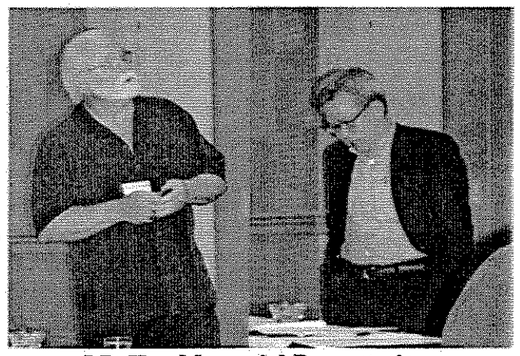
"generalized linear latent and mixed models". All courses were lectured by experienced and excellent instructors. On Monday, June 13th, Dr. Scheuren, the President of American Statistical Association open up the symposium with his keynote speech "Outreach to other national statistical societies". In 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.

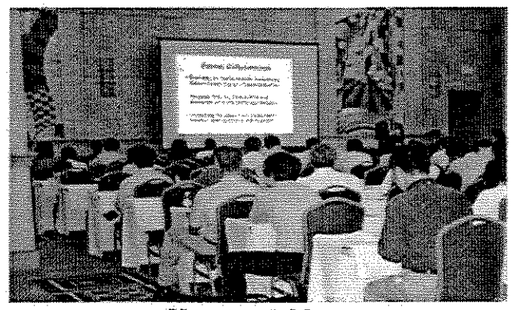
Now after a 12 month planning and developing, the symposium is carried out smoothly and the event is over. The experience we shared is both important and unique. I will treasure this experience with pride and gratefulness. I want to say it again to all my colleagues that worked on this symposium project,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



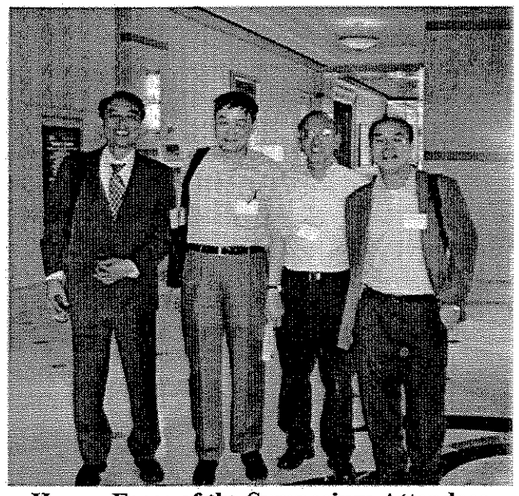
One of the Short Courses



J.P. Hsu Memorial Presentations



Keynote Address



Happy Faces of the Symposium Attendees

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/BLS/ 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. **[SELECTED PUBLICATIONS]** Dr. Shao is the author or coauthor of more than 120 research articles published in various journals between 1987 and 2004. Many of these articles focus on statistical methodology for asymptotic inference, the jackknife, bootstrap, balanced half samples, model selection, missing data, and imputation, while many others consider bioequivalence, drug shelf-life estimation, and other statistical applications in clinical trials. Dr. Shao wrote two textbooks for Ph.D. study in statistics, *Mathematical Statistics* (1999) and *Mathematical Statistics: Exercises and Solutions* (2005), both published by Springer. He is also a coauthor of three statistical methodology monographs, *The Jackknife and Bootstrap* (1995) published by Springer, *Statistics in Drug Research* (2002) and *Sample Size Calculations in Clinical Research* (2003) published by Marcel Dekker.

[ICSA ACTIVITIES] Publication Committee Chair (1998, 2004, 2005); Board of Directors of ICSA (2000-2002). **[RELATED PROFESSIONAL ACTIVITIES]** Dr. Shao has been an associate editor for *Statistica Sinica* since its inception in 1991. He is also an associate editor for *Journal of American Statistical Association* (1993-1996, 1999-2005) and a coeditor for *Journal of Multivariate Analysis* (2002-present) and *Sankhya* (2002-present). Dr. Shao is a Fellow of The Institute of Mathematical Statistics (1996) and a Fellow of The American Statistical Association (1999), and a life-time member of ICSA. **[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 unselfish 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 American. Our goal is to make the ICSA as a truly international statistical body to which the entire statistical society 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 compliment 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

[PRESENT POSITION] Associate Director, Office of Biostatistics, 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).
[ICSA ACTIVITIES AND OFFICES HELD] Editor-in-Chief of ICSA Bulletin (2000-2002); Member of Publication Committee (2000-2002), Member of Board of Directors (2002-2004), Member of Awards Committee (2002-2004), Chair of Biometrics Section (2003). "Controversial Statistical Issue" Special Section Editor, ICSA Bulletin (2003-2005). Served as the chairs, organizers, invited speakers in ICSA Applied Statistical Symposium (1996, 1997, 1999, 2001, 2002, 2004, 2005). Chair, J.P. Hsu Special Invited Session, 2005.
[RELATED PROFESSIONAL ACTIVITIES] Dr. Wang is a member of ICSA and ASA. Her related professional activities in the various statistical, clinical, bioninformatics, 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 statistics, pharmaceutical 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-moderated in the Tracks of "Pharmacogenomics 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 the 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 Bulletin is one of the most popular statistical newsletters, ICSA 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 (Josh)
[PRESENT POSITION] Senior Biometrician, Clinical Biostatistics, Merck Research Laboratories, PA **[FORMER POSITION]** Biometrician, Clinical Biostatistics, Merck Research Laboratories, PA **[DEGREE]** Ph.D. in Statistics, University of Wisconsin-Madison, 2000; M.S. in Probability and Statistics, Peking University, Beijing, 1995; B.S. in Probability and Statistics, Peking University, Beijing, 1992. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Group sequential methods, adaptive designs, survival analysis, HIV clinical trials. **[PUBLICATIONS]** "Monitoring mortality at interim analyses while testing a composite endpoint at the final analysis", Controlled Clinical Trials 2003, with D.L. DeMets and K.K.G. Lan; "Increasing the sample size when the unblinded interim result is promising", Statistics in Medicine 2004, with D.L. DeMets and K.K.G. Lan; "Incorporating durability information in the comparison of proportions of patients with HIV suppression", Journal of Biopharmaceutical Statistics 2004, with M.L. Nessly and B. Thiyagarajan; "Treatment comparisons for a partially categorical outcome applied to a biomarker with assay limit", Statistics in Medicine 2005, with A.L. Gould and M.L. Nessly; "Model-based correction to QT interval for heart rate for assessing mean QT interval change due to drug effect", Drug Information Journal 2005, with G.C.G. Wei. Other collaborative publications on medical journals. **[ICSA ACTIVITIES]** Member of ICSA; Volunteer for ICSA. **[PROFESSIONAL SERVICES]** Member of ASA. Chaired a session on Adaptive Design in 2003 JSM. Reviewer for Statistics in Medicine and Journal of Biopharmaceutical Statistics.

CHEUNG, Siu Hung
[PRENSENT POSITION] Associate Professor, Department of Statistics, The Chinese University of Hong Kong. **[FORMER POSITION]** Assistant Professor (1991-1994), Department of Statistics, The Chinese University of Hong Kong. Visiting Fellow, Department of Statistics and Applied Probability, National University of Singapore (1997-1999).

[DEGREES] Ph.D. in Statistics, 1991 Temple University; MS in Statistics, MA in Sociology, 1987, University of Georgia. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Multiple comparison procedures, Adaptive designs, Time series and Statistics education. **[SELECTED PUBLICATIONS]** "Multiple testing to establish superiority/equivalence of a new treatment compared with k standard treatments for unbalanced designs", *Biometrics,* 2004, with KS Kwong and WS Chan; "Multiple comparisons with a control in families with both one-sided and two-sided hypotheses", *Statistics in Medicine*, 2004, with KS Kwong, WS Chan and SP Leung; "Family-wise Robustness Criteria for Multiple Comparisons Procedures", *Journal of the Royal Statistical Society - Series B*, 2002, with B. Holland.**[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, Milton Chung-lien

[PRESENT POSITION] Senior Mathematical Statistician, Division of Biometrics II, Office of Biostatistics, Center for Drug Evaluation and Research, Food Drug Administration, Rockville, Maryland. **[FORMER POSITION]** Mathematical Statistician (1979-1987) Bureau of Census, Suitland, Maryland; Member of Staff Fellow (1974-1979) Computer Sciences Corp, Silver Spring, Maryland; Consultant (1973-1974) Consultants and Designers Co., N.Y., N.Y. **[DEGREE]** Ph.D. in Mathematical Statistics; George Washington University, 1986; M.A. in Statistics, University of Rochester, 1971; B.S. in Mathematics, Fu Jen Catholic University, Taiwan, 1967. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** biostatistics, clinical trails, logistic regression, meta analysis, non-inferiority, adaptive design, imputation estimation; census and sampling survey. **[PUBLICATIONS]** "Experience with Historical Control Data in NDA Submission from a FDA Reviewer's Perspective', ASA Biopharmaceutical Proceeding, 1997, with M.F. Huque; "Ridit Analysis of Ordered Categorical Response Data for Small Sample", ASA Biopharmaceutical Proceeding, 1990, with Y. Tsong; "Evaluation of the 1980 Census Precanvass Coverage Improvement Operations", ASA Survey Research Method Proceeding, 1984, with J.H. Thompson; "Sample Design, Estimation, and Presentation of Sampling Errors for the 1980 Census Provisional Estimates of Social, Economic, and Housing Characteristics", ASA Survey Research Method Proceeding, 1982, with J.H. Thompson, J. Kim and H.F. Woltman; "1980 Census Variance Estimation Procedure", ASA Survey Research Method Proceeding, 1981, with H.F. Woltman, S.M. Miskura, and J.H. Thompson. **[PROFESSIONAL SERVICES]** member of ASA since 1970; founding member and permanent member of ICSA. **[ICSA ACTIVITIES]** Member of Executive Committee and Treasurer, ICSA 2005 Applied Statistical Symposium.

LI, W.K.

[PRESENT POSITION] Chair Professor, Department of Statistics & Actuarial Science, since 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). **[Honour]** Elected Fellow of the American Statistical Association, 2003 **[FIELD OF MAJOR STATISTICAL ACTIVITIES]** Time Series Analysis. **[SELECTED PUBLICATIONS]** Book: "Diagnostic Checks in Time Series", Chapman & Hall, 2004; Papers: "An Adaptive Estimation of Optimal Regressor Subspace (with discussion)," 2002, J. Royal Stat. Soc. B; "Estimation for Partially Nonstationary Multivariate Autoregressive Models with Conditional Heteroscedasticity," 2001, Biometrika; "On a Mixture of Autoregressive Conditional Heteroscedastic Model," 2001, J. Amer. Stat. Assoc.; "On a Mixture Autoregressive Model," 2000, J. Royal Stat. Soc. B; "On Single-Index Coefficient Regression Models," 1999, J. Amer. Stat. Assoc.; "Limiting Distribution of Maximum Likelihood Estimators for Unstable ARMA Time Series with GARCH errors," 1998, Annals of Statistics; "On

Fractionally Integrated Autoregressive Moving Average Time Series Models with Conditional Heteroscedasticity," 1997, J. Amer. Stat. Assoc.; "Testing Model Adequacy for Some Markov Regression Models for Time Series," 1991, Biometrika; "A Goodness of Fit Test in Robust Time Series Modelling," 1988, Biometrika; "Fractional Time Series Modelling," 1986, Biometrika; "Diagnostic Checking ARMA Time Series Models Using Squared-Residual Autocorrelations," 1983, J. Time Series Analysis; "Distribution of Residual Autocorrelations in Multivariate ARMA Time Series Models," 1981, J. Royal Stat. Soc. B. **[ICSA OFFICES & ACTIVITIES]** Program Committee (2002-2007); Chairman, Organizing Committee of the 5th ICSA International Conference, Hong Kong, (Aug. 2001). **[PROFESSIONAL ACTIVITIES]** President, Hong Kong Statistical Society (2000-2001, 2001-2002, 2002-2003). **[ASSOCIATE EDITORSHIP]** Statistica Sinica; Applied Stochastic Models in Business and Industry.

LOU, W.Y. Wendy

[PRESENT POSITION] Canada Research Chair in Statistical Methods for Health Care; Associate Professor, Department of Public Health Sciences, University of Toronto, Toronto, Canada. **[FORMER POSITION]** Assistant and Associate Professor, Department of Biomathematical 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 STATISTICAL ACTIVITIES]** Runs 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. **[SELECTED PUBLICATIONS]** Articles: "On runs and longest run tests: method of finite Markov chain imbedding", Journal of the American Statistical Association (1996); "On the probability of pattern matching in nonaligned DNA sequences", with JC Fu and SC Chen, in *Scan Statistics and Applications* (1999); "A new measure for continuity of care: the Alpha index", Health Services and Outcomes Research Methodology (2001). Book: *Distribution Theory of Runs and Patterns and Its Applications: A Finite Markov Chain Imbedding Approach*, with JC Fu, World Scientific Publishing (2003). Papers in other statistical and biomedical science journals, including Annals of the Institute of Statistical Mathematics, Statistica Sinica, Canadian Journal of Statistics, Statistics and Probability Letters, Communications in Statistics, Journal of Applied Probability, Journal of Nuclear Medicine, Radiology, American Journal of Preventive Medicine, Journal of the American Academy of Dermatology, Respiratory Medicine. **[ICSA ACTIVITIES]** Permanent member of ICSA; Local program chair, ICSA Annual Meeting (1994); Speaker, ICSA International Statistical Conferences and Applied Statistics Symposiums. **[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; PI and Co-PI 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 POSITION]** Assistant and Associate Professor (1992-2003) Department of Statistics, The Pennsylvania State University, State College, PA. **[DEGREE]** Ph.D in Statistics, University of Chicago, 1992; M.S. in Statistics, University of British Columbia, 1989; B.S. and M.S. in Automatic Control and System Sciences, Beijing Institute of Technology, Beijing, China, 1982, 1986. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Generalized Linear Models. Estimating Equations. Dimension Reduction. Semiparametric Estimation and Inference. Asymptotic Theories and Methods. Longitudinal and Clustered Data Analysis. **[PUBLICATIONS]** Professor Li has published 27 papers including Wong, W.H. and Li, B. (1992). Laplace expansion for posterior densities of nonlinear functions of parameters. Biometrika, vol 79, 393-8; Li, B. (1993). A deviance function for the quasi likelihood method. Biometrika, vol 80, 741-753; Li, B. and McCullagh, P. (1994). Potential functions and conservative estimating functions.Annals of Statistics, vol 22, 340-356. Murphy, S. and Li, B.

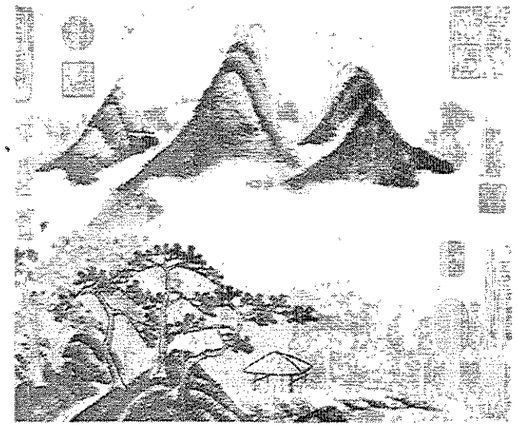
(1995). Projected partial likelihood and its application to longitudinal data. Biometrika, vol 82, 399-406. Li, B. (1996). A minimax approach to consistency and efficiency for estimating equations. Annals of Statistics, vol 24, 1283-1297. Lindsay, B. and Li, B. (1997). On second-order optimality of the observed Fisher information. Annals of Statistics, vol 25, 2172-2199. Li, B. (1998). An optimal estimating equation based on the first three cumulants. Biometrika, vol 85, 103-114. Qu, A. Lindsay, B., and Li, B. (2000). Improving generalized estimating equations using quadratic inference functions. Biometrika, vol 87, 823-836. Cook , R.D. and Li , B. (2002). Dimension reduction for conditional mean in regression. Annals of Statistics, vol 30, 455-474. Chiaromonte, F. Cook, R. D. and Li , B. (2002). Partial dimension reduction with categorical predictors. Annals of Statistics. vol 30, 475-497. Li, B., Cook, R.D., Chiaromonte, F. (2003). Dimension reduction for conditional mean in regression with categorical predictors. Annals of Statistics. vol 31, 1636--1668. Cook, R.D. and Li, B. (2004). Determining the dimension of Iterative Hessian Transformation. Annals of Statistics. vol 32. Li, B., Zha, H. and Chiaromonte, F. (2005). Contour regression: a general approach to dimension reduction. Annals of Statistics (to appear). **[PROFESSIONAL SERVICES]** Member of the program committee for the Joint Statistical Meetings at Dallas, Texas, 1998; Session organizer for The Eighth International Conference of the Forum for Interdisciplinary Mathematics, Wollongong, Australia, December, 2001; Session organizer for the SRCCS (Statistical Research Center for Complex System) 2004 International Workshop for Statistics , Seoul, Republic of Korea, 2004; National Science Foundation Panelist; Associate Editor, Journal of Statistical Planning and Inference.
[ICSA ACTIVITIES]
Program organizer for the IMS Asian and Pacific Regional Meetings at Taipei, Taiwan, 1997.

SHAO, Qi-Man
[PRESENT POSITION] Professor, Department of Mathematics, Hong Kong University of Science and Technology (starting in June 2005), Guang-Biao Professor, Zhejiang University (starting in June 2005), and Associate Professor, Department of Mathematics, University of Oregon. **[FORMER POSITION]** Professor, National University of Singapore, Professor, Hangzhou Univeristy. **[DEGREE]** Ph.D in Probability and Statistics, University of Science and Technology of China (1989), M.S. in Probability, Hangzhou University (1986) and B.S. in mathematics, Hangzhou University (1983). **FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Self-normalized large deviation theory, Limit theory, Gaussian processes, Monte Carlo study, Change point analysis. **[PUBLICATIONS]** Professor Shao has published over 100 papers in probability and statistical journals, including Ann. Probab., Probability Theory and Related Fields, Ann. Stat., JASA, and Biometrika. **[HONORS]** *Fellow* of Institute of Mathematical Statistics. **[PROFESSIONAL SERVICES]** Associate Editor, Ann. Stat (2003-); Associate Editor, Probability Surveys **[ICSA ACTIVITIES]** Permanent Member of ICSA; Member of Program Committee, Sixth ICSA conference.

Peter Xue-Kun Song
[PRESENT POSITION] Associate Professor, Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, Canada. **[FORMER POSITION]** Assistant and Associate Professor (1996-2004), Department of Mathematics and Statistics, York University, Toronto, Canada. Associate Visiting Professor (2002-2003), Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan. **[DEGREE]** Ph.D in Statistics, University of British Columbia, 1996; M.S. in Applied Mathematics, SW Jiaotong University, 1987; B.S. in Statistics, Jilin University, China, 1985. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Biostatistics, Generalized linear models, longitudinal data analysis, time series analysis and statistical computing. **[PUBLICATIONS]** Professor Song has published over 30 papers in statistical methodological and applied journals, including JASA, Biometrika, Biometrics, Scandinavian Journal of Statistics, Canadian Journal of Statistics, Statistics in Medicine, Journal of Financial Econometrics, Sankhya, Journal of Biopharmaceutical Statistics, and Journal of Applied Probability. **[PROFESSIONAL SERVICES]** Member, IMS New Researchers Committee (2003-2005); Program Chair and Chair of Local Organizing Committee, the 7th IMS New Researchers Conference, 2004; Chair of the Canadian National NPCDS project on Longitudinal and Clustered Data Analysis, 2005. Director of Statistics Division (2003-2004), Department of Mathematics and Statistics, York University, Toronto. **[ICSA ACTIVITIES]** Regular attendee of ICSA Applied Statistics Symposia.

WANG, Suojin
[PRESENT POSITION] Professor of Statistics and Epidemiology&Biostatistics, Texas A&M University, College Station, TX. **[FORMER POSITIONS]** Assistant and Associate Professor (1990-1998), Texas A&M University. Visiting Professor (1998-1999), University of Southampton, University of Geneva, and Swiss Federal Institute of Technology; Senior Research Fellow (1994), Bureau of Labor Statistics; Visiting Assistant Professor/Research Associate (1988-1990), Southern Methodist University. **[DEGREES]** Ph.D in Statistics, University of Texas at Austin, 1988; B.A. in Mathematics, Hangzhou (now Zhejiang) University, 1982. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Biostatistical inferences; Bootstrap and other resampling methods; Missing and mismeasured data analysis; Nonparametric regression methods; Saddlepoint approximation; Survey sampling. **[PUBLICATIONS]** Dr. Wang has published over 80 refereed papers in major statistical and health sciences journals, including Biometrika, JASA, JRSSB, Annals of Statistics, Statistica Sinica, Bioinformatics, Biometrics, Journal of Applied Probability, SIAM Journal on Numerical Analysis, Journal of Econometrics, Technometrics. Annals of the Institute of Statistical Mathematics, Journal of Computational and Graphical Statistics, Scandinavian Journal of Statistics, Survey Methodology, Journal of Rural Health, Journal of Medical Directors Association, Pharmacoepidemiology and Drug Safety, Journal of Palliative Medicine. **[HONORS]** Fellow of the American Statistical Association; Fellow of the Institute of Mathematical Statistics; Elected member of the International Statistical Institute; TAMU College of Science Faculty Distinguished Teaching Award. **[ICSA ACTIVITIES]** Permanent Member of the ICSA; Active participant of the ICSA activities including its conferences and symposiums. **[RELATED PROFESSIONAL ACTIVITIES]** Associate Editor of Biometrics (1997-); Editorial board member of Journal of Nonparametric Statistics (2004-); Associate Editor of Communications of Statistics (1995-2001); NSF Review Panelist; President, Vice-President and Secretary of the Southeast Texas Chapter of the ASA (1991-1994); TAMU Faculty Senator (1997-1998).

Hu, Mingxiu
[PRESENT POSITION] Associate Director, Pfizer Inc., New London, CT, since 1998 **[FORMER POSITION]** Sr. Statistician, Synectics, Washington, DC, 1995~1998. **[DEGREE]** Ph.D in Statistics, George Washington University, 1998; M.A. in Biology, Brown University, 2004; M.S. in Statistics, Beijing Unviersity, 1992. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Longitudinal data analysis, cumulative meta-analysis, clinical trial design, imputation methods, statistical simulation, and in vitro/in vivo correlation modeling **[PUBLICATIONS]** Dr. Hu has published 15 papers in statistical, clinical, and pharmaceutical science journals, including Statistics In Medicine, American Journal of Clinical Pathology, Statistica Sinica, Communications in Statistics, Pharmaceutical Research, Biological Psychiatry, Statistics and Probability Letters, etc. **[PROFESSIONAL SERVICES]** ASA Membership Committee (2004~2008); ASA Connecticut Chapter Executive Committee (2002~2006), Vice President/ Program Chair of ASA Connecticut Chapter (2004-2005) and expect to be the President of the Chapter (2005~2006). Manuscript reviewer for Biometrics, Statistica Sinica, Drug Information Journal, Journal of Agricultural, Biological, and Environmental Statistics, and Journal of Pharmaceutical Statistics **[ICSA ACTIVITIES]** Program Committee member for 2006 Applied Statistics Symposium.



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 Liou 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://venus.stat.sinica.edu.tw/ss/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 for 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 themed 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 Sinca entitled "The Statistics of Brain Imaging". In addition to the three speakers: Professor Moo Chung 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 2003 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 this opportunity to serve our community, as it has been a gratifying experience, which we will carry with fond memory.

Hwai-Chung Ho, Ph.D., is Research Fellow of the Institute of Statistical Science, Academia Sinica, Taipei, Taiwan, R.O.C.
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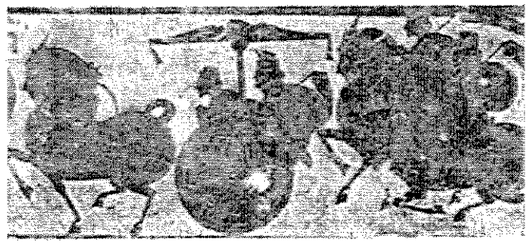
Jane-Ling Wang, Ph.D., is Professor of Statistics, University of California, Davis, CA, U.S.A.
Email: wang@wald.ucdavis.edu



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Bayesian Inference, Environmental Statistics, Time Series Analysis, and their Applications

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 "9 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，得到先父啟蒙，又得到中學、大學和研究院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，受到周邊環境的影響。歷史上未曾出現過一個大科學家在沒有文化的背景裏，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累積下來的成果，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，也不可能漠視幾千年來偉大學者共同努力得來的成果，這是人類瞭解大自然，了解人生，了解人際關係累積下來的經驗，不是一朝一夕所能夠成就的。這些經驗透過不同的途徑在當代學者的行為和著作中表現出來，不同文化背景的學者在接受先人的文化，在接受同儕的交流時會有不同的反應。有深厚的文化背景，有胸襟的學者比較容易汲取多元化的知識，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，學者又能盡量發展個人的意志思維，因此孕育了影響西方文明二千多年的哲學和科學，他們在一、兩百年間集中了一群學者，談天論地，求真求美，將當時積聚的知識有系統的整理出來，他們的精神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、向東拓地的結果，夏商周三代的文化與各地的地方文化融合，學者受到各種文化的衝擊，拓展出中華民族原創作能力的高峰。承受先朝的文化是中華民族優良的傳統，孔子就說過：「周監於二代，郁郁乎文哉」，孔丕都很重視「存亡國，繼絕世」的做法。在中國本土上，文化綿綿不斷數千年，可說是全世界絕無僅有的。

秦承七國的文化經驗，開始了完備的典章制度。漢唐又繼承這個傳統，並得到西域和印度文化的融合，達到中國極盛時期。宋朝國力雖然積弱，但在科技上有極大的突破，四大發明都是這一段時間的創作。

從宋朝到今日已經一千年了。近二百年來中華民族受到外國的衝擊可說是前古所未有的。而這廿年來國家經濟的穩定發展終於使我們民族能夠安定下來，我們年青人對祖國開始有信心，也開始想一些重要的民生以外的問題，希望在這個時候，中華民族和西方文化，能夠得到自然的融合，而併發出一個求善、求真、求美的新文化。司馬遷自傳說：「先人有言，自周公卒，五百歲而有孔子，有能紹明世、正易傳，繼春秋，本詩書禮樂之際，意在斯乎，意在斯乎，小子何敢讓焉。」由於時代的發展，能夠承先啟後、融合東西的事業，恐非一人一時之力所能完成。然而諸位都知道，在具有天時、地利、人和的環境裏，事情會來得順利。回想當年量子力學研究剛開始時，不能不感嘆一時多少豪傑。縱觀今日科技的發展，只要找到好的方向，在好的氣氛栽培薰陶下，人人都可能成為豪傑。

做學問的抱負：

故大學問必需有高尚的情操，以下五點最為重要：

一、 求不朽之業：

左傳 《叔孫豹論三不朽》

太上有立德，其次有立功，其次有立言，雖久不廢，此之謂不朽。

曹丕 《典論 論文》

蓋文章，經國之大業，不朽之盛事。年壽有時而盡。榮樂止乎其身。二者必至之常期，未若文章之無窮。是以古之作者，寄身於翰墨，見意於篇籍，不假良史之辭，不托飛馳之勢，而聲名自傳於後。

史記 《孔子世家傳》

天下君王至于賢人，眾矣。當時則榮，沒則已焉，孔子布衣，傳十餘世，學者宗之，自天子王侯。中國言六藝者，皆折中於夫子。

二、 承先啟後的使命感：

《文心雕龍》 諸子篇

身與時舛，志共道申。標心於萬古之上，而送懷與千載之下。

史記 《太史公自傳》

春秋之作：夫春秋，上明三王之道，下辨人事之紀……

史記之作：……余當掌其官，廢明聖盛德不載，滅功臣世家，賢大夫之業，墮先人所言，罪莫大焉。

西方偉大的巨著如 Euclid 和 Newton 都是承先啟後的作品。

三、 有所見，有所思，而啟示諸眾人，傳諸後世。

孔子：孔子知言之不用，道之不行……丘恥沒世而無聞焉。

司馬遷《報任安書》：此人皆意有郁結，不得通其道也，故述往事，思來者。……僕誠已著此書，藏之名山，傳之其人，通邑大都。

脂批《紅樓夢》：字字看來皆是血，十年辛苦非尋常。

曹雪芹：滿紙荒唐言，一把辛酸淚。

四、 由於濃厚的好奇心驅使，希望憑觀察、推理，來瞭解大自然的結構，尋找宇宙的真諦。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，才做得更好一點。相對論和量子力學就是人類因為好奇而產生的。科技上的創新也跟好奇心有關，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基於數學家濃厚的好奇心而引發。

五、 科學家和文學家為了尋找一個美的結構，可能窮畢生的精力。近代的統一場論，某些晶體結構、數論或幾何上種種雅致的命題，都引起熱烈的研究，而追尋純美則是這種研究的主要動力。黎曼幾何的創始即為一例。

學者並不見得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通路：

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通訊方法的研究都因為軍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、 很多學者以追尋榮譽為主要的原動力，諾貝爾獎金確實使很多年青科學家拚力去做科學研究。這種榮譽不見得單是個人的榮譽，也可以是民族的榮耀。當年李楊得獎，全國興奮，影響了兩代人。

大致上來說很少學者能夠很單純的只有一個學習的原動力，往往有很多原因和背景使他們成長。但是傳世不朽之作，必定有包含第一到第五點的考慮才能夠完成，上述 Turing 和 Wiener 等大師在純科學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、權力為主要原動力的學習，當目的達到後，很難再持續下去。不幸的是，大部份的中國學者都以此為目標。

學習的方向受到我們立志的影響，得到師友的薰陶後，擇善而固執之，始可成大器。

社會文化和師友對學者的影響：

事實上，社會的文化對我們有深刻的影響。三百年以前，中國士大夫看不起外國蠻夷之邦，以為他們不讀聖賢書，整個民族自傲而不實事求是地去觀摩別人的長處。等到兵敗割地後才開始反省，影響到五四運動的全盤西化。這是大時代的變遷，在這個時代長大的學者很難不隨波逐流，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。

例如美國東北方有很多學者仍然有着濃厚的清教徒作風，有如中國人所說的狷介之士。從前孔子在陳，有歸與之嘆：「歸與，歸與，吾黨之小子狂簡，斐然成章……」就是因為狷介之士有可取的地方。很多清教徒願意為了自己堅信的理念來犧牲生活上的舒適，為學問而做學問，自強不息。

蘇聯的學者就比較粗獷；德國和日本學者則心細謹慎；而美國這一百年來的成就在於兼收並蓄，集思廣益。這是自古以來，一個國家推動學問成功的最重要因素，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，都聚集了大量的人材。孔子出於魯國，到司馬遷時仍然見到「諸生以時習禮其家」，人材的匯聚確可以移風易俗。

在學校裏，往往見到教授在發展富有原創性的發明，屢次嘗試都不成功，最後成功時他的喜悅會使學生們覺得興奮，也想自己來一點類似的經驗。有時會看到兩個教授持不同的意見互相批評對方學說的缺點，學生會受到這種氣氛的感染，認識真理的重要性，瞭解創造的趣味。

我們又可以看到一群年青的學生和教授肆無忌憚的去走前人未走過的路。當一群有熱情、有能力的人都在做研究的時候，大部份人都會受到感染而跟着去闖。

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，「吾私淑諸人也」就是這個意思。學問既然是累積的，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，即使飽學之士亦然：

陶淵明

好讀書，不求甚解，每有會意，便欣然忘食。

這一點很重要：即使有困難，也要自強不息，讀書能夠欣然忘食是成功的一大步。對學問的感情能夠專一濃厚自然會有成就。從前屈原、司馬遷、李煜等人的作品都極富感情，王國維說他們的作品出於赤子之心，以血書成，千載以後，仍然為他們的作品感動不已。當愛因斯坦創立相對論時，滿腔熱情的來找尋引力場的最自然架構。Watson 在他的自傳裏提到他和 Crick 在找尋 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要的幾何結構、Watson 對所需要的 X-ray 折射理論都並非專家，都是憑一股熱情，而摸索成功的。

現舉屈原的著作來描述他的專誠：

亦余心之所善兮，雖九死其猶未悔。

當我們找到喜愛的方向時，絕不輕言放棄。

屈原

民生各有所樂兮，余獨好修以為常，
雖體解吾猶未變兮，豈余心之可懲。

我記得從前為了解決一個很重要的問題時，朝思暮想，有如詞賦所說：

宋徵宋

天遙地遠，萬水千山，知他故宮何處，怎不思量，除夢裏有時曾去。

柳永

惟鄧路之遼遠兮，魂一夕而九遊。

當感情豐富時，即使開始時不求甚解，經過不斷的浸淫，真理亦會逐漸明朗。但是感情豐富，必需有師友的激勵。

師者傳習授業解惑者也。
三人行，必有我師焉。
學而時習之，不亦樂乎。

找尋學問的方向：

通過學習，或與師友切磋，或與古人神交，視野才會廣闊，才會放棄自己以前一些瑣碎的想法，去找尋學問的重要方向。

晏殊
……昨夜西風凋碧樹，獨上高樓，望盡天涯路。

能夠放棄不重要的研究，而去思考自己的路向，需要有踏實的基礎，有好的文化修養、氣質、同時不怕別人譏笑。

涉江
苟余心其端直兮，雖僻遠之何傷。

韓愈　答李翊書
始者非三代兩漢之書不敢觀，非聖人之志不敢存，處若忘，行若遺，儼乎其若思，茫乎其若迷。當其取於心而注於手也，惟陳言之務去，戛戛乎其難哉！其觀於人，不知其非笑之為非笑也。如是者亦有年，猶不改。然後識古書之正偽，與雖正而不至焉者，昭昭然白黑分矣，而務去之，乃徐有得也。當其取於心而注於手也，汩汩然來矣。其觀於人也，笑之則以為喜，譽之則以為憂，以其猶有人之說者存也。如是者亦有年，然後浩乎其沛然矣。吾又惧其雜也，迫而距之，平心而察之。其皆醇也，然後肆焉。雖然，不可以不養也。行之乎仁義之途，遊之乎《詩》、《書》之源，無迷其途，無絕其源，終吾身而已矣！

學習和思考並進：

找尋自己學問的路向，必需要保持濃厚的好奇心，要不停的發問。中國古代最有名的發問的文章是：

屈原天問
遂古之物，誰傳道之，上下未形，何由考之……日月安屬，列星安陳？

但是以後中國學者讀聖賢書，不敢質問聖人的言行和天地間的物象了。

即使做學問的大方向決定後，中間不可能沒有很多疑難的地方，此時有老師「傳道授業解惑」是很有幫忙的，而更應當的向師友切磋發問：

善問者如叩鐘，問之大者則大鳴，問之小者則小鳴。

上面兩個不同的發問，一個是「思考」，一個是「學習」，實在應當並重才能夠成功。

論語
學而不思則罔，思而不學則殆。

我們對每個學說需要「求因」、「明變」和「批判」，才能夠將整個學說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。

一個好的學者，需要不斷的觀察大自然的現象，從人類累積得來的經驗中尋找天同的定律，加以驗證、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。

苦學：

無論是那位大文學家或大科學家，都離不開勤苦學習的階段。

屈原
路曼曼其修遠兮，吾將上下而求索。

柳永
衣帶漸寬終不悔，為伊消得人憔悴。

苦學而能持久，並非易事，最忌的是「一鼓作氣，再而衰，三而竭。」中國小孩讀書往往小學時就盡力，到大學時已經力竭了。

為學另一件忌怕的是基本修養不久，而好議論別人長短來掩飾自己的弱點。

從失敗中找出路：

在苦學和思考之後，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，就如同出征、或打敗仗或遇伏，都是一個考驗我們的修養的時候。

司馬遷評管仲
其為政也，善因禍而為福，轉敗而為功。貴輕重，慎權衡。桓公實怨少姬，南襲蔡，管仲因而伐楚，責包茅不入貢於周室……諸侯由是賓齊。

從失敗的經驗中找到成功的路子，是做研究的不二法門。因為嘗試各種途徑時，往往失敗的多，成功的時候少，但是我們做研究時走過的路很少是浪費的，有時做的研究給人搶先做去，可以從對方的文章中得到啟發，做一篇更有意義的文章，或者可以看出這些研究不值得去做。取捨的問題，不單是關乎經驗，亦關乎學者的氣質。

學問與氣質的培養：

關於氣質，我們先看：

曹丕　《典論 論文》
譬諸音樂，曲度雖均，節奏同檢，至於引氣不齊，巧拙有素，雖在父兄，不能以移子弟。

表面上，做大學問必需要天才才能成功。其實並不盡然：

<u>*《琴苑要錄》*</u>

伯牙學琴於成連，三年而成，至於精神寂寞，情之專一，未能得也。成連曰：吾學不能移人之情，吾師有方子春，在東海中。乃齎糧從之，至蓬萊山。留伯牙曰：「吾將迎吾師」，刺船而去，旬時不返。伯牙心悲，延頸四望，但聞海水汩沒，山林窅冥，群鳥悲號，仰天歎曰：「先生將移我情。」乃援琴作歌。

從這裏可以看出氣質亦可以培養，在吸收多元的文化後，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就開始。司馬遷的文章氣吞江河，就是因為他父親從小就讓他「西至空桐，北過涿鹿，東漸於海，南浮江淮。」又送他到齊魯之地學古文並跟董仲舒唸書，所以太史公的早熟是有原因的。

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，又博覽群書，就昂昂然無所懼怕了。

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，或志向不純，學業就很容易枯萎。

<u>*離騷*</u>

何昔日之芳草兮，今直為此蕭艾也。
豈其有他故兮，莫好修之害也。

<u>*曹丕*</u>

貧賤則懾於飢寒，富貴則流於逸樂。

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賈誼：

<u>*王勃*</u>

屈賈誼於長沙，非無聖主，豈乏明時。

<u>*蘇軾評語*</u>

王者之佐，……非漢文之不能用生，生之不能用漢文也。

其後以自傷哭泣，至於夭絕，是亦不善處窮者也。夫謀之一不見用，則安知終不復用也？不知默默以待其變，而自殘至此。嗚呼！賈生志大而量少，才有餘而識不足也。

有人學識不足，而妄求上位；有人才學過人，竟妄自菲薄，或自傷不遇，這都是其文化修養未逮，胸襟不闊之故。

以天為師：可以明天理，通造化。
以人為師：可以致良知，知進退。

文章的風格與個人的修養：

我們的修養往往從問題的取捨、方向的堅持、行文遣字、計算簡繁中表現出來。在科學和數學的研究中就有這個現象。

楊振寧先生就曾指出偉大的科學家如 Dirac 和 Heisenberg 文章的風格不同。在數論上，Siegel 和 Weil 都有偉大的創作，但是風格迥異，這大概與他們出身和經歷有關，即使在找尋真理時，我們的修養會影響到我們吸收和瞭解真理的能力。

除了地域外，時間的變化也很明顯的影響我們的風格。我們都知道一時代有一時代的文學，科學亦然，例如二十世紀中葉的數學講究抽象和嚴格，現在已經不講這一套了。

讀書的風氣、研究的態度，會在科研的文章表現出來，也可以看到民族的潛力。這一點可和音樂比較，從音樂中可以看國家的盛衰。

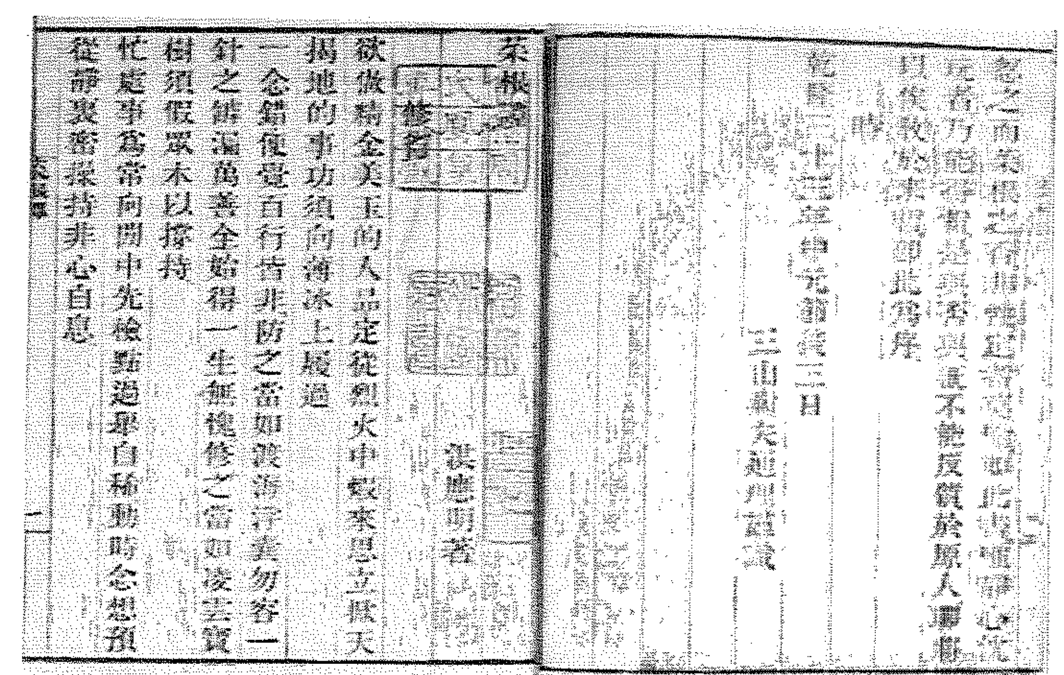
<u>*左傳　《季札觀周樂》*</u>

吳公子札來聘，請觀於周樂，使工為之歌周南，召南。曰「美哉，始基之矣，猶未也，然勤而不怨矣。」……為之歌鄭，曰「美哉，其細已深，民弗堪也，是其先亡乎。」為之歌齊，曰「美哉，已泱泱乎，大風也哉，表東海者，其太公乎，國未可量也。」……

從這裏我們可以知道培養氣質的重要，有志做大學問的學者更要注重培養氣質，人的志向，師友和社會文化的影響都需要重視。當一個學者操守不正，只求名利，只求權柄時，辭氣自然衰微，難見到偉大的結構了。

最後，僅以數語相贈：

行乎名利之途，入乎公卿之門，雖榮受賞，吾不謀也。
得乎造物之真，樂乎自然之趣，雖窮有道，文其興乎。


菜根譚
修省
洪應明著
欲做精金美玉的人品定從烈火中煅來思立掀天揭地的事功須向薄冰上履過
一念錯便覺百行皆非防之當如渡海浮囊勿容一針之罅漏萬善全始得一生無愧修之當如凌雲寶樹須假眾木以撐持
忙處事為常向閒中先檢點過舉自稀動時念想預從靜裏密操持非心自息
三山病夫通理識

京都弦学[1]之会记

世纪之初，仲夏七月。四方学者，远渡扶桑，会同两京俊彦，聚於旧都，谈弦入微，论天修道。江口[2]逢迎，大栗[3]引路。卫腾[4]说法，鲁士[5]颂弦。史公[6]宏道，威化[7]献工，问宇称超凡，费玻二子何时可对[8]。究矩阵模式[9]，宏观场论[10]何时可用。费海[11]翻腾，众士尤争新意。质子衰变[12]，时空岂能无定。士才五百[13]，敢揭太初之谜，弦仅十七[14]，却奏和乐之章。喜真理之渐明，启大道於未央。遂颂其事如左。

美哉山川，壮哉民智。葱葱竹林，郁郁松树。渺渺白云，巍巍古寺。浪涛如涌，列屿似鳝[15]。日升东海之端，僧参禅宗之义。筵供众神於长庙兮记天竺之故事，奉大佛於奈良兮传盛唐之遗意[16]。金阁辉煌，银阁雅致。彰帝国之朱华[17]，赏风月之无边。清水寺上，殿若经台。望月楼头，歌宴舞榭。登高塔以望远兮临深池之倒照。展砂石之古朴兮醉圆林之禅意。溪水潺流，微雨纷飞。暮鼓晨钟，犹是千古流风，夙兴夜寐，尚在大和魂中。岂无玄想，冥思高山之颠。岂乏知音，切磋小湖之边。核力介传，汤川[18]所钟。量化重整，朝永[19]所工。高木[20]西访，数数学之明珠。小平[21]东渡，宏几何之大观。吁嗟乎壮哉，日出之国。维新未远，已国众学之基。二战仓皇，尚求造物之渊。惜乎共和虽在，王道稍微。纵九天光华，难释友邻苦衷[22]。算佛法慈悲，犹待众生普渡。水深兮鱼悦，林茂兮鸟鸣。岂圣哲之所宗，无以敦友邦[23]。抑科学之所加，非以睦斯民[24]。奚不宏忠厚以为教，觅无怨以为基[25]。喜莫喜兮欢乐共，乐莫乐兮真理通。祝友谊之永固兮盼来者之可追，实吾心之所善兮无日夜其忘之。

夫宇宙之多容，自遥古而恒变，光阴之长流，结天地其未分。何太初之渺渺，须臾而生万象[26]。抑原爆之洪洪，余波[27]犹振天际。大哉美哉，引力之场。无远而弗届，积小而定天。长空漫漫，星河灿灿，聚尘埃兮生辉，重自身兮湮灭[28]。何曲率之盈盈，观流光而睹乙象[29]。黑物[30]冥冥，灌大空其犹未识。浩浩乎，大块犹涨[31]，频动谱红[32]。赫赫乎，星河互冲，云卷天崩。星旋何急，波引何柔[33]。白热为心，银汉肆其扩张。黑洞为疆，时空岂其未伤[34]。渺兮困兮，宇宙之数[35]，结构之谜。远兮茫兮，诸天之道，众物之途。人世杳杳，天道悠悠。星河亿兆，生机唯地可寻。物象万千，理念合人难释[36]。惟光之恒速，未关乎观者[37]。质之换能，溯源於相对[38]。既得乎等价之义，相对之则。何可却曲率为力，几何为基[39]。小则测光子之途，大则观拓扑之变[40]。穷数理之所能，犹惑大千泰否。苟真相之可知，虽九死其何可悔。

地极有磁，云阴生电。性分甫殊，宛若参商。何生何属，何连何结。光子为禹媒[41]，方程为姻[42]。电何生辉，法则有源。磁独有偶，单极难求[43]。力场有势，规范是依。宇称为圆，拓朴载荷[44]。善引力之不如，万物方其有踪[45]。苟光阴之能虚[46]，磁电孰其可分[47]。既基础之已知，岂任用之难期。电流机转，磁浮车飞。声传万里，减却相思无数。线结千山，尽见灯火如聚。何百载科研，泽民若是[48]。怅人间寒热，扶持犹待。

奇哉妙哉，量子之学。融波兮成粒，见波兮知机[49]。山岳未成其障[50]，鬼神岂难其测[51]。何相对之量化，知电子能反，微子自旋[52]。唯电子跃跳，使周期可解[53]，分子成结。物律富於畴昔，新意解得旧谜。道有阴阳，力分强弱。弱力玻传，衰变能识左右[54]。强力胶坚，色动犹有璨味[55]。何天下之至微，囿於至细，三份始克成粒[56]，三家适可成象[57]。嗟微子之多元，叹宇称之能规。范群不换，万象始知纯美[58]。质量其何，众士犹觅真意[59]。场论早成规矩，实验若合符节。岂三力之齐一，实造物之有常。何量化之难求，抑引力之未卜[60]。唯至小能窥大，因至美而知真。道湛湛其深妙，遂千古之所宗[61]。

使微子为弦，振动如音[62]。行踪翻成曲面，量化始知共形[63]。费玻同列[64]，积分竟其可驯[65]，真空微扰，引子自然而生[66]。十维时空，弦学始其不迷[67]。四力齐驱，几何示其大观[68]。微空卷曲，拓扑为质。何理论之多元，对偶系而为一[69]。实真空之众繁[70]，基础未知唯象。造物宏图，未可窥於一旦。筹学妙处，庶几传诸永世[71]。路曼曼其修远，吾将上下而求索。

嗟夫，弦会已矣，哲人归去。西国科研，未融中土。东亚心学，犹在儒佛。多人事兮众心负荷，小物理兮万象无常。求究本源，奚以知物性而通造化。未知物性，何以制万象以泽斯民。曷不奇心基础之学，置身自然之中。苟真美之可知，孰天人之难合[72]。

信京都之琼美兮，吾实爱乎故乡。山嶷峨峨，大溪茫茫。长河菲菲，东海苍苍。何国土之芬芳兮叹山河之壮丽。吾先君之所居兮祖茵裔之所息。居异域而怀乡兮身一载而九还[73]。登高楼以远望兮国中兴以向荣。祈天之纯命兮广我百姓视听。祷地之所给兮足我民族立命。盼士之志洁兮孰德言之可无，惟心无际涯兮实东西之可翻[74]。享我国魂兮，真美是献。

丘成桐

二零零四年三月二十九日

注释：

[1] 弦学，指起於 1987 年的超弦理论。

[2] 江口，日本理论物理学家 Eguchi.

[3] 日裔理论物理学家 H. Ooguri.

[4] 美国理论物理学家，费尔兹奖获得者 E. Witten。

[5] 美国理论物理学家，2004 年诺贝尔奖获得者 D. Gross。

[6] 美国超弦理论学家，A. Strominger。

[7] 伊朗裔美国超弦理论学家 C. Vafa。

[8] 费玻二子指费米子（Fermion）和玻色子（Boson），前者服从 Fermi 统计，数学上用反对易的费米数来描写，後者服从 Bose 统计，用普通数描写之。当二者对称地出现理论中时，场论或弦论可出现超对称。

[9] 矩阵模型.

[10] 弦论的低能有效理论是非微扰场论。

[11] 费海，指费米子海，是 1929 年 DIRAC 引入的相对论性量子真空观念。

[12] 质子衰变实验，是检验强—电—弱大统一理论的实验。理论预言原子寿命在 10^{32} 年以下，而实验却发现在 10^{35} 以上，此事至今为悬案。

[13] 约五百人参加日本京都弦论会议.

[14] 会议安排日本音乐家演奏 17 弦线之日本歌.

[15] 京都风景优美，令人神往。

[16] 在唐代佛学由中国传到日本，在日本留下许多寺庙，佛像。

[17] 京都是日本的故都。

[18] 汤川秀树，日本理论物理学家，约於 1935 年提出由介子传播核力的理论，於 1954 年获诺贝尔物理学奖。

[19] 朝永振一郎，日本理论物理学家，约 1947 年首创量子电动力学的重整化理论，1969 年获诺贝尔物理学奖。

[20] 日本数学家高木贞治早年在德国留学，回日本後发展希尔伯特的类域论，成为代数数论的重要一章。

[21] 小平邦彦是日本数学家。二战后到普林斯顿访问，对大范围几何，特别是复几何有突破性的贡献，于 1954 年获得菲尔兹奖。

[22] 日本二战期间对邻国造成的痛苦，尚未得到谅解。

[23] 中日两国文化背景相似，认同这个背景易和睦相处。

[24] 发展科学有利于社会的和谐。

[25] 中国传统文化中忠厚，宽容（恕）是非常基本的观念。

[26] 宇宙始於 147 亿年前的大爆炸。

[27] 微波背景辐射。

[28] 星体质量凝聚到一定程度演变成黑洞。

[29] 引力透镜效应.

[30] 指弥漫和充斥在宇宙中的暗物质。

[31] 宇宙在膨胀，近几年的观测建议宇宙在加速膨胀。

[32] 宇宙学红移或哈勃红移，由於宇宙膨胀而导致的红移。

[33] “星旋”指星系的旋转，“波引”指引力波。

[34] 黑洞是时空视界，含时空奇点。

[35] 宇宙常数是很小的正数（存在暗能量）是目前困扰科学家的基本难题。

[36] 宇宙中星系繁多，只有在地球上发现生命。而宇宙学的理论都是人类创造的。

[37] 光速不变原理，狭义相对论的基本原理之一。

[38] 相对论预言了质能关系：$E=mc^2$

[39] 爱因斯坦用几何奠定了广义相对论的基础。等效原理是广义相对论的基本原理之一。基本方程由局域不变性等要求导出，力用曲率表示，其优美和深刻令人惊叹。

[40] 确定光的轨迹和时空的大范围性质等都要用几何。

[41] 光子是传播电磁相互作用的基本粒子，是以圆群为规范群的规范场。

[42] 麦克斯韦方程将电，磁统一，是描述电磁相互作用的基本方程。

[43] 到目前为止，磁单极子仍然只是理论预言。

[44] 拓扑上的非平凡空间可给出物理上的荷。

[45] 引力在和电弱尺度相比很小的尺度下才起作用，这样物质才可以动。

[46] 指场论中的 Wick 转动，把时间虚化，带来许多方便。

【47】 若在物理上时间真是虚的，电磁就不可分辨了。

[48] 电磁学给人类带来许多应用，改变了我们的生活。

[49] 量子力学中波函数可以解释为几率。

【50】 量子隧道效应，经典解若非最低能量态在量子系统都是不稳定的。

【51】 测不准原理。在小尺度下，坐标和动量无法同时被确定。

[52] 相对论量子力学预言了粒子自旋和反粒子的存在。

【53】化学中的周期表可以用电子跃迁解释。

[54] 弱相互作用通过交换中间玻色子传递，此时左右对称性破缺。

[55] 量子色动力学是描述强相互作用的基本理论，通过缪子传递相互作用。夸克带色、味两种量子数。

[56] 指量子色动力学 SU(3)规范对称性。

[57] 粒子物理标准模型包含三代夸克和三代轻子。

[58] 杨-Mills 的规范不变性是基本粒子标准模型的基础。

[59] 基本粒子的质量计算有很大的人为性，希望能从更深的理论导出。

[60] 在前面三种物质场中，引力是作为背景场出现的，未考虑其量子化。引力的量子化对于研究极小尺度（普朗克尺度）是至关重要的。

[61] 电、弱、强相互作用统一在以规范场为基础的标准模型下，堪称人类认识自然的典范。

[62] 在弦论中粒子由弦的振动模式描述。

[63] 弦在时空中的运动轨迹画出一两维曲面，其上的理论只和曲面的形状有关，与大小无关，这即所谓两维共形场论。

[64] 在弦论中引入超对称，玻色子与费米子处於对称地位，此谓超弦理论。

[65] 困扰物理学家的量子场论中的无穷大问题因点粒子用弦代替而解决。

[66] 引力自然出现在弦理论的自洽性条件中。

[67] 超弦理论在十维时空才是自洽的。

[68] 弦理论的最初动机是强相互作用的模型 後人们意识到它是统一四种相互作用的合适理论。

[69] 1995-1996 年人们发现了弦的非微扰态，由此得到五种微扰弦理论是相互等价的，此谓对偶。

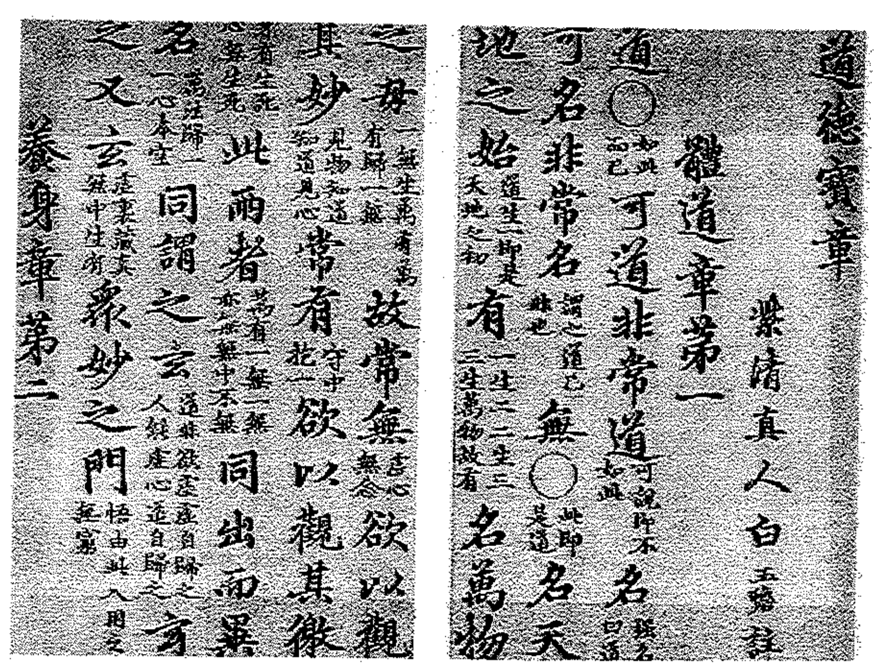
【70】 弦理论中出现繁多的真空态，这对应用弦理论到具体的物理模型中带来很大的困难。

[71] 丘先生发现的 Calabi-Yau 空间，初为数学中的一美妙结果，後在弦理论的内禀空间的主要模型。弦论，作为引力的量子理论，和数学密不可分。

[72] 不重视基础研究，民心将鲁钝，社会将腐化，不利於国家的发展。

【73】丘先生每年都回国讲学许多次，为发展中国的学术事业竭尽全力。

[74] 融合东西文化，不应带有任何偏见，宜以宽广胸怀去芜存精。



Special Feature Article:
An Introduction to Financial Econometrics

By: Jianqing Fan, Ph.D.
Department of Operation Research & Financial Engineering, Princeton University

What is the financial econometrics?

This simple question does not have a simple answer. The boundary of such an interdisciplinary area is always moot 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. lumbers, corns, soybeans), a farmer may enter into the future contracts of the commodity; to reduce the risk of weather exposures, amuse 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 undergraduate 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
12. Nonparametric methods in financial econometrics

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 predicable. 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 lost 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 it 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 Δ, 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 $\Delta = .458$. 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 and loss or 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 rises to new financial econometrics problems. We will discuss some of these issues in the stochastic modeling section. 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

dividend yields. See Ait-Shahlia 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 baring 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 select 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 Goureroux 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 litter 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-Ingsoll-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 rises 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 return 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

[1] Ait-Sahalia, Y. and Lo, A. W. (1998). Nonparametric estimation of state-price densities implicit in financial asset prices. Journal of Finance, 53, 499-547

[2] Black, F. and Scholes, M. (1973). The pricing of Options and Corporate Liabilities. Journal of Political Economy, 81, 637-659.

[3] Campbell, J.Y., Lo, A. and MacKinlay, A. C. (1997). The Econometrics of Financial Markets. Princeton University Press, Princeton, N.J.

[4] Carroll, R.J., Ruppert, D. and Stefanski, L.A. (1995). Measurement Error in Nonlinear Models, Chapman and Hall, London.

[5] Cochrane, J.H. (2001). Asset Pricing, Princeton University Press, Princeton.

[6] Duffie, D. (2001). Dynamic Asset Pricing Theory (Third Edition). Princeton University Press, Princeton, New Jersey.

[7] Engle, R. F. (1995). ARCH, selected readings, Oxford University Press, Oxford.

[8] Fan, J. (2003). A selective review of nonparametric methods in financial econometrics. www.princeton.edu/~jqfan.

[9] Fan, J. and Yao, Q. (2003). Nonlinear Time Series: Nonparametric and Parametric Methods. Springer-verlag, New York.

[10] Gourieroux, C. and Jasiak, J. (2001). Financial Econometrics: Problems, Models, and Methods. Princeton University Press, Princeton.

[11] Gourieroux, C., Monfort, A. and Renault, E. (1993). Indirect Inference . Jour. Appl. Econometrics, 8, supplement, S85-S118.

[12] Hansen, L. P. (1982). Large sample properties of generalized method of moments estimators, Econometrica, 50, 1029-1054.

[13] Hull, J. (2003). Options, Futures, and Other Derivatives (Fifth edition). Prentice Hall, Upper Saddle Review, New Jersey.

[14] Jorion, P. (2000). Value at Risk: The new benchmark for managing financial risk (2nd ed.), McGraw-Hill, New York.

[15] Lintner, J. (1965). The valuation of risky assets and the selection of risky investments in stock portfolios and capital budgets. Review of Economics and Statistics, 47, 13-37.

[16] Markowitz, H. (1959). Portfolio Selection: Efficient Diversification of Investments. John Wiley & Sons, New York.

[17] Merton, R. (1973a). Rational theory of option pricing. Bell Journal of Economics and Management Science, 4, 141-183.

[18] Merton, R.C. (1973b). An intertemporal Capital Asset Pricing Model. Econometrika, 41, 867-887.

[19] Ross, S. (1976). The arbitrage theory of capital asset pricing. Journal of Economic Theory, 13, 341-360.

[20] Ruppert, D. (2004). Statistics and Finance: An Introduction. Springer-Verlag, New York.

[21] Sharpe, W. (1964). Capital asset prices: A theory of market equilibrium under conditions of risks. Journal of Finance, 19, 425-442.

[22] Shephard, N. (2004). Stochastic volatility: selected readings. Oxford University Press.

[23] Tsay, R.S. (2002). Analysis of Financial Time Series. John-Wiley & Sons, Inc., New York.

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 $Z_w = \sqrt{w}Z_I + \sqrt{1-w}Z_{II}$, where w is a constant weight ($0 \le w \le 1$). A typically natural weight is $w = N_{(1)}/N$, where $N_{(1)}$ is the sample size for stage I and N is the originally plan total sample size. The sample size for stage II, $N_{(2)}$ can be chosen after observing Z_I. There are different rules for the choice for $N_{(2)}$, such as:

(a) If the real treatment effect is the same as observed in Stage I, choose $N_{(2)}$ so that the unconditional power would be the same as planned (Cui, Hung, and Wang, 1999).

(b) If the real treatment effect is the same as observed in Stage I, choose $N_{(2)}$ 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 I, choose $N_{(2)}$ so that the sponsor can afford and 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 $N_{(2)}$ 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 $N_{(2)}$ takes, the α-level will be preserved if the weighted Z-test is employed for the final analysis. That is, Z_w is standard normal under the null hypothesis, and thus the α-level critical value of Z_w is still z_α.

Researchers have shown that, under rule (a) above, there exists a classical group sequential design which is more efficient that the two-stage weighted-Z design (Tsiatis and Metha, 2003). However, the weighted Z-test could be applied to different rules in practice. First of all, by pre-specifying rule (a), Z_I can easily be found out from the choice of $N_{(2)}$ 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 $N_{(2)}$. It is flexible as the two Z 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 $N_{(2)}$ may do. The null hypothesis is rejected if the weighted Z-test Z_w 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 desired rule doesn't need to be fixed in advance, increasing sample size will not

reveal interim observed Z_I value, therefore, the concerns of data integrity and potential bias can be addressed satisfactorily. Since there are so many different choices for $N_{(2)}$, 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 $N_{(2)}$ 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 Trost (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 α-level will be inflated.
- If the study stops early for futility because the conditional power is low, then the α-level will be reduced.

As long as the inflation does not exceed the deflation, the α-level will be maintained. An interim sample size re-estimation procedure is outlined below. Data is analyzed at the information time τ, 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 $\le$ *ll (lower limit)*, stop and accept the null hypothesis H_0.
(2) If CP $\ge$ *u (upper limit)l*, continue to $\tau = 1$. Reject the null hypothesis H_0 if the un-weighted $Z_{\tau=1} \ge z_\alpha$.
(3) If *ll* < CP < *ul*, extend the trial to $\tau = m > 1$ so that after extension, the conditional power CP*m* = *ul*. Reject the null hypothesis H_0 if $Z_{\tau=m} \ge z_\alpha$.

As reported in Lan and Trost (1997), for $\tau = 0.5$, *ll* = 0.1, *ul* = 0.85 and $\alpha = 0.025$ ($z_{0.025} = 1.96$), the probability of type I error with this procedure, estimated by simulations with 1 million repetitions, 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 $\tau = 0.5$, and the sponsor may choose *ll* different from 0.1, or *ul* different from 0.85. However, further simulation suggested that when $\tau \le 0.7$, *ul* ≥ 0.5 and *ll* ≥ 0.1, and use a critical value of 1.96 for the final test, the α-level will be kept under 0.025. As a result, if the sponsor is willing to stop for futility when *ll* $\ge$ 0.1 and the interim look is taken place when $\tau \le 0.7$, the α-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 many 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.

References

[1] Chen, YHJ, DeMets, DL, and Lan, KKG. Increasing the sample size when the unblinded interim result is promising. *Statistics in Medicine*, 2004, 23:1023-1038.
[2] Cui, L, Hung, HMJ, and Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics*, 1999, 55:321-324.
[3] Fisher, LD. Self-designing clinical trials. *Statistics in Medicine*, 1998, 17:1551-1562.
[4] Lan, KKG and Trost, DC. Estimation of parameters and sample size re-estimation. *American Statistical Association Proceedings of the Biopharmaceutical Section*, 1997.
[5] Tsiatis, AA and Mehta, CR. On the inefficiency of the adaptive design for monitoring clinical trials. *Biometrika*, 2003, 90:367-378.

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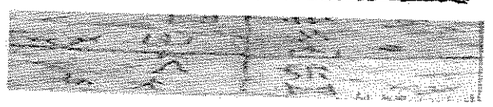

Issues in Breast Cancer Therapy

Kao-Tai Tsai, Ph.D.

Cancer remains as one of the most deadly disease. 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 CIRB. 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,

$$N_t = N_0 \exp[\log(N_\infty / N_0)(1-\exp(-bt))]$$

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, topoisomerases inhibitors, mitosis inhibitors, etc., (2) Hormonal therapy, which includes Steriods, anti-estrogens, anti-androgens, LH-RH analogs, anti-aromatase agents, and (3) Immunotherapy, which includes inteferon, interleukin-2, and vaccines. For breast cancer, the most commonly used agents are tamoxifin, 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: neutropenia, anemia, nausea/vomiting, diarrhea, alopecia,

peripheral neuropathies, mucositits, and arthralgia/myalgia, etc. The causes of side effect is that the anticancer drugs 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 is the combined effect may be better than the simple 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 adjuvant 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, cancer 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 patient with symptomatic disease requiring a quicker response. However, for patients whose cancer relapsed after adjuvant therapy, the combination chemotherapy such as docetaxel or capecitabine 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 divisive:

Clinical Situation	Combo.	Seq.
Asymptomatic patients with bone metastases	23%	77%
Asymptomatic patients with several small lung metastases	30%	70%
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	85%	15%

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		
	No prior Rx	AC-paclitaxel	(> 2yrs)
AC	29%	-	
FAC/FEC	26%	6%	3%
Capecitabine/docetaxel	16%	64%	61%
AT (either taxane)	16%	3%	6%
Platinum agent/docetaxel	3%	9%	9%
Capecitabine/paclitaxel	-	3%	6%

However, there seems to be a majority agreement that doctaxel 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%	30%	3%
Paclitaxel	20%	2%	2%
Capecitabine	8%	33%	23%
Vinorelbine	-	20%	33%
Gemcitabine	2%	8%	35%
Doxorubicin	5%	5%	2%
Cyclophosphamide	-	-	2%
Platinum	-	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; genes; 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:

NBIOPS	Age	
	< 50 yr	>=50 yr
0	1	1
1	1.698	1.273
>=2	2.882	1.620

AGEMEN	>=14	12-13	< 12
	1	1.099	1.207

NUMREL	AGEFLB			
	<20	20-24	25-29	>= 30
0	1	1.24	1.55	1.93
1	2.61	2.68	2.76	2.83
>=2	6.79	5.77	4.91	4.17

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.

NBIOPS	Age	
	< 50 yr	>= 50 yr
0	1	1
1	1.80	1.62

AGEMEN	>= 14	12-13	< 12
0	1	1.05	1.10

NUMREL	AGEFLB			
	<20	20-24	25-29	>= 30
0	1	1.16	1.33	1.54
1	1.59	1.80	2.04	2.32
>=2	2.52	2.81	3.12	3.48

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, anther trial, STAR trial, is trying to compare Tamoxifen with Raloxifene of there effects in cancer prevention.

Chemotherapy General settings

As mentioned previously, neoadjuvant therapy is applied prior to operation, and ajuvant 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 chemo, taxanes, and combination regimens. It is still unknown that preoperative 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 setting 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.

References

Gail, M., et al., "Projecting Individualized Probabilities of Developing Breast Cancer for White Females Who Are Being Examined Annually," JNCI, 1989.

Costantino, J., et al., "Validation Studies for Models Projecting Invasive and Total Breast Cancer Incidence," JNCI, 1999.

Jenny C Chang, et al "New Gene expression profiling for the prediction of therapeutic response to docetaxel in patients with breast cancer," The Lancet, 2003.

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At Cross-Purposes: Cross-Over Trials in Theory and Practice

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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, beta-agonists, 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 obtain, 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, 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 a 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 naïve and some is also 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 by treatment interaction (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 that 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 given the result 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 Donev 1996; John, 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. Since 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 many 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 have 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 engendering 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 treatments(Fleiss 1986; 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 that assumes carry-over from A into A is the same as from A into B makes no sense. Although these criticism 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(Kunert 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, the 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 interaction 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 carry-over 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 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 close to despair sometimes when 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 at all that does not address 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, Hashimoto et al. 1991) and 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 examining the concentration 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) criticising 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 subjunctive but applied statistical models need a grounding in reality.
2. Do not press your design or analysis as a solution to the practical problems of the practising scientist until you have acquired some familiarity with his or her field of research.
3. Biology matters.

Reference

Fleiss, J. L. (1986). "Letter to the editor." Biometrics **42**: 449-450.

Fleiss, J. L. (1989). "A critique of recent research on the two-treatment cross-over design." Controlled Clinical Trials **10**: 237-243.

Fletcher, D. J., S. M. Lewis, et al. (1990). "Factorial designs for crossover clinical trials." Statistics in Medicine **9**(10): 1121-1129.

Freeman, P. (1989). "The performance of the two-stage analysis of two-treatment, two-period cross-over trials." Statistics in Medicine **8**: 1421-1432.

Grizzle, J. E. (1965). "The two-period change over design and its use in clinical trials." Biometrics **21**: 467-480.

Hills, M. and P. Armitage (1979). "The two-period cross-over clinical trial." British Journal of Clinical Pharmacology **8**: 7-20.

John, J. A., K. G. Russell, et al. (2004). "CrossOver: an algorithm for the construction of efficient cross-over designs." Statistics in Medicine **23**(17): 2645 - 2658.

Jones, B. and A. N. Donev (1996). "Modelling and design of cross-over trials." Stat Med **15**(13): 1435-46.

Jones, B. and M. Kenward (2003). Design and Analysis of Cross-over Trials. London, Chapman and Hall.

Kunert, J. and J. Stufken (2002). "Optimal crossover designs in a model with self and mixed carryover effects." Journal of the American Statistical Association **97**(459): 898-906.

Senn, S., G. D'Angelo, et al. (2004). "Carry-over in cross-over trials in bioequivalence: theoretical concerns and empirical evidence." Pharmaceutical Statistics **3**(2): 133-142.

Senn, S. J. (1992). "Is the 'simple carry-over' model useful? [published erratum appears in Statistics in Medicine 1992 Sep 15;11(12):1619]." Statistics in Medicine **11**(6): 715-26.

Senn, S. J. (1996). The AB/BA cross-over: how to perform the two-stage analysis if you can't be persuaded that you shouldn't. Liber Amicorum Roel van Strik. B. Hansen and M. de Ridder. Rotterdam, Erasmus University: 93-100.

Senn, S. J. (2002). Cross-over Trials in Clinical Research. Chichester, Wiley.

Senn, S. J. and F. Ezzet (1999). "Clinical cross-over trials in phase I." Stat Methods Med Res **8**(3): 263-78.

Senn, S. J. and D. Lambrou (1998). "Robust and realistic approaches to carry-over." Statistics in Medicine **17**(24): 2849-64.

Sheiner, L. B. (1991). "The intellectual health of clinical drug evaluation [see comments]." Clin Pharmacol Ther **50**(1): 4-9.

Sheiner, L. B., Y. Hashimoto, et al. (1991). "A simulation study comparing designs for dose-ranging." Statistics in Medicine **9**: 1287-1302.

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Non-inferiority: The Recent 5-year Odyssey

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For the recent five years the statistical literature on non-inferiority has grown tremendously; see the selected references of Hung, Wang and O'Neill (2005) and the 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 undoubtedly the literature does shed many important insights into the unique essence of each statistical method and would hopefully help clinical scientists see the end of a seemingly infinite tunnel.

For ease of presentation, let me use alphabetical letter to represent both a treatment group and its expectation of the interested response. Denote by T-C the effect of the new treatment T relative to the concurrent positive control C. The same discussion as to be articulated below can also be pertinent to the treatment effect in terms of ratio, not just difference. From historical data, we have the parameters C_0 and P_0 of the selected positive control and the placebo, respectively. For the last five years, we have at least learned that the most popular non-inferiority hypothesis is that 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 H_0: $T-C \leq -0.5(C-P)$ and thus the relevant non-inferiority margin is $\delta = -0.5(C-P)$. This hypothesis is not testable from the data of the current non-inferiority trial where the placebo arm does not exist. Only when $C-P = C_0-P_0$ (often referred as to 'constancy assumption'), the estimate of (C_0-P_0) in the historical trials can be used to help test this hypothesis. The constancy assumption can only be judged subjectively by faith or belief; 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 rescue.

With a point estimate and a confidence interval for the effect of the control, C_0-P_0, in the past, the major task is to choose a number that is, at best, an estimate so that the chosen estimate is equal to the margin δ of which the value is unknown. This is a statistically impossible task. Our clients (mostly medical colleague) rarely know the clinical margin but 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_0-P_0). Why 95%? At least, it covers the true value of (C_0-P_0) 95% of the times, namely, 95% out of many many replicates of the historical trials. However, given the chosen lower limit of the 95% confidence interval from the existing historical trials, what is the probability that the true value of (C_0-P_0) 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 (C_0-P_0) into the non-inferiority inference as stipulated by Hung et al. (2005). For example, the probability of falsely asserting the 50% retention can be assessed on the basis of this probability averaged over the distribution of the (C_0-P_0) 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., $\geq$ 95%) confidence interval of (T-C) 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 unconditional 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 $\geq$95% confidence interval for the parameter (T-C) + 0.5(C-P) that is directly associated with the 50% retention hypothesis (recall H_0: T-C $\geq$-0.5(C-P), equivalently, T-C + 0.5(C-P) $\geq$0). 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), Snapinn (2004). If the 95% confidence interval is above zero, then one can assert the 50% retention with the type I error probability of at most 5%. Had a placebo arm been studied in the non-inferiority trial, the synthesis approach would have been most efficient. Without the placebo arm, one can only estimate (C-P) by the historical estimate of (C_0-P_0), assuming the constancy assumption holds. Here comes a problem. 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 percent 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 and is desperately needed 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), imagining that there are many active control trials in the same patient population using the same active control, averaging all (C-P)'s and (C_0-P_0) 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 resulting average. 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 control effect C-P from the past to the future. However, there will unlikely be any future data for C-P and the only data we have for C-P is from the estimates of C_0-P_0. While updating the location of C-P, the data remains at the estimates of C_0-P_0. The placebo effect also stays at the estimates of P_0 without future data to updating it. If the placebo effect P 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".

Acknowledgment
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Disclaimer
The views expressed in this article do not necessarily represent those of the U.S. Food and Drug Administration.

Reference
Hung, H.M.J., Wang, S.J., O'Neill, R.T. (2005). A regulatory perspective on choice of margin and statistical inference issue in non-inferiority trials. *Biometrical Journal* 47, 28-36.
Hung, H.M.J., Wang, S.J., Tsong, Y., Lawrence, J. and O'Neill, R.T. (2003). Some fundamental issues with non-inferiority testing in active controlled clinical trials. *Statistical in Medicine* 22, 213-225.
Holmgren, E.B. (1999). Establishing equivalence by showing that a prespecified percentage of the effect of the active control over placebo is maintained. *Journal of Biopharmaceutical Statistics* 9(4), 651-659.
Hasselblad, V. and Kong, D.F. (2001). Statistical methods for comparison to placebo in active-control trials. *Drug Information Journal* 35, 435-449.
Wang, S.J., Hung, H.M.J., Tsong, Y. (2002). Utility and pitfall of some statistical methods in active controlled clinical trials. *Controlled Clinical Trials* 23, 15-28.
Wang, S.J. and Hung, H.M.J. (2003a). TACT method for non-inferiority testing in active controlled trials. *Statistical in Medicine* 22, 227-238.
Wang, S.J. and Hung, H.M.J. (2003b). "Assessment of treatment efficacy in non-inferiority trials", *Controlled Clinical Trials* 24, 147-155.
Rothmann, M., Li, N., Chen, G., Chi, G.Y.H., Temple, R.T., Tsou, H.H. (2003). Non-inferiority methods for mortality trials. *Statistics in Medicine* 22, 239 - 264.
Snapinn, S.M. (2004). Alternatives for Discounting in the Analysis of Noninferiority Trials. *Journal of Biopharmaceutical Statistics* 14, 263-273.
Hung, H.M.J. (2001). Non-inferiority: a dangerous toy? *Bulletin of the International Chinese Statistical Association*, January issue, 27-29.
Lawrence, J. (2005). Some remarks about the analysis of active control studies. *Biometrical Journal* (to appear).
Simon, R. (1999). Bayesian design and analysis of active control clinical trials. *Biometrics* 55, 484-487.

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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 in 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 efficacy claim. It is worthwhile 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 and misleading signal in favor of the claim that the drug is effective when in fact it is not, 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, in other words, a false negative result. In the language of hypothesis testing this is 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 used is as follows[1]. A test statistic 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. This probability 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 that 0.05. It represents a way of producing a quantification of the strength of evidence[2, 3] 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. An 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[4]. Primary endpoints are primary focus of a trial. Their results determine main benefits of the trial's study intervention. Secondary endpoints on the other hand are considered not sufficient for characterizing benefits of the treatment[5]. They are generally tested for statistical significance for extended indication and labeling purposes after the primary 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 1 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 to test, 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 control to a desired 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[6]. 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 results that are generally meant 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 configurations 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 of total mortality. No efficacy for total mortality combines 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 without 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 conclude 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 primary 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, the win criterion, and the statistical analyses methods, and are likely to produce un-interpretable 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-Cognitive Sub-scale endpoint and the endpoint that measures Clinician's Interview Based Impression of Change. In this case, the null hypothesis is a union null hypothesis that asserts that there is no efficacy of the intervention simultaneously for both endpoints; the alternate hypothesis 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., $\alpha = 0.05$).

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 MI, or stroke. In this case the null hypothesis is an intersection 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 (win on both *drop attack rate* and 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[7]). Thus, seizure rate can be tested at a significance level of $\alpha = 0.025$, and also attack rate and the seizure severity each can be tested at the same significance level of 0.025. This will control FWER strongly at the significance level 0.05.

Concluding Remarks

Multiplicity problem 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 to 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

1. Cox, D. R.; Hinkley, D.V. *Theoretical Statistics*, page 66, Chapman and Hall, London, 1974
2. Kempthorne, O; Folks, L. *Probability Statistics, and Data Analysis*, page 314, Iowa University Press, Ames, Iowa, 1971
3. Huque, M.F; Al-Osh, M; Dubey, S.D. P-values, evidence, and multiplicity considerations for controlled clinical trials. *Encyclopedia of Biopharmaceutical Statistics*, Marcel Decker, Inc., New York, 2003.
4. Moye, L.A. *Multiple Analyses in Clinical Trials,* pages 110-119, Springer-Verlag, New York, 2003
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
6. Hochberg, Y; Tamhane, A.C. *Multiple Comparison Procedures*. John Wiley & Sons, New York, 1987.
7. Moye, L.A. Alpha calculus in clinical trials: considerations and commentary for the new millennium. *Statistics in Medicine 2000*, **19**: 767-779

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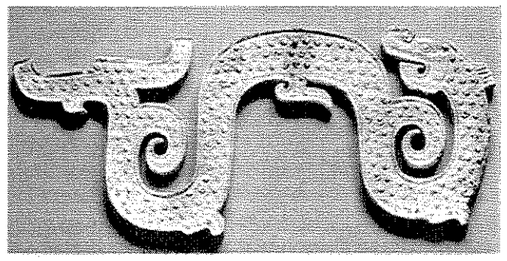

*Commentary on Alpha Allocation Design Strategies in Clinical Trials Using Genomic Signature **

Sue-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 adapt 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/genetics to identify the therapeutic effect hinges on an appropriate identification of a genomic composite biomarker (GCB).[1] 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[2] 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 sample sizes for the all-comer and GCB-present patients (Wang, 2005)[3]. 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 studied 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 hypothesis.

Tarceva[R] (erlotinib) Tablets[4] 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 I/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. A post-hoc interest, following the approval of Iressa[R] (gefitinib)[5] 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 turns 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

0.93) in the remaining patients whose EGFR status cannot be determined or do not have the tissue samples collected. Note that 15% of the patients were EGFR–, 17% EGFR+, and 68% without EGFR status determined.

Without pre-specification of the defined subgroup hypothesis, the valid statistical inference is limited in the investigation of Tarceva EGFR subgroup effect. Had Tarceva EGFR+ subgroup hypothesis been pre-specified, the above three general strategies for alpha-allocation would have been valid allowing for scientifically and statistically valid inference of the Tarceva EGFR subgroup testing.

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Disclaimer: The views presented in this article do not represent those of the U.S. FDA.

References

1. Simon R, Wang SJ (2005). Use of Genomic Signatures in Therapeutics Development. The Pharmacogenomics Journal. Under Review.
2. Simon R (2005). Conducting definitive Phase III trials using pharmacogenomics. The 3rd DIA-FDA-PWG-PhRMA-BIO Pharmacogenomic workshop, April 12, 2005, Rockville, MD.
3. Wang SJ (2005). Alpha allocation design strategy in pharmacogenoimc trials using genomic biomarker. ICSA Applied Statistics Symposium, June 13, 2005, Rockville, MD.
4. Tarceva Labeling Package Insert (2004).
5. Iressa (gefitinib) Labeling Package Insert (2003).

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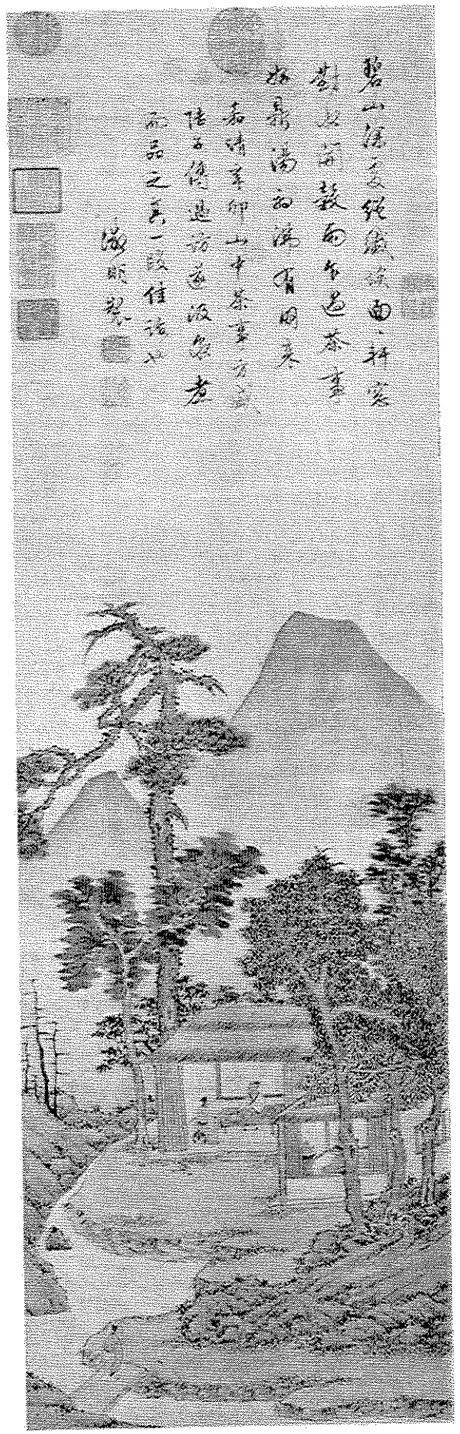

Regional Activities

Hong-Kong

Hailiang 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 include15 well known statisticians. The scientific committee chairmen are Jianqing Fan (Princeton University) and Fred J. Hickernell (Hong Kong Baptist University) and the local organising 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 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/

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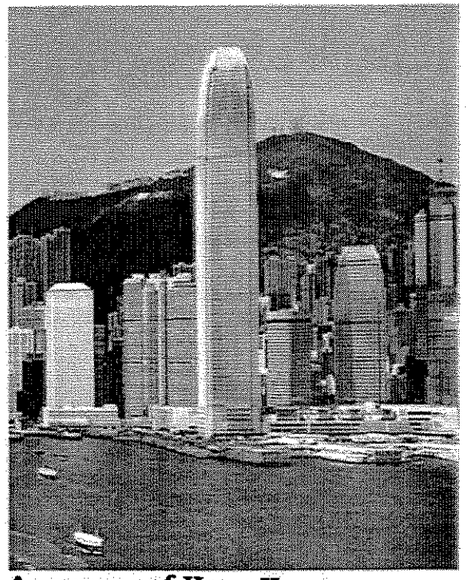

A scenery of Hong Kong

Taiwan

C. Andy Tsao, Ph.D.

Recent Statistical Conferences and Workshops in Taiwan

The 2005 Southern Taiwan Statistical Conference and Chunghwa Data Mining Society Annual Meeting.
June 25—26, National Cheng Kung University, Tainan. URL: http://www.stat.ncku.edu.tw/2005/

2005 Statistics Camp for Undergrads
June 28—29. Academia Sinica, Taipei.
URL: http://www.stat.sinica.edu.tw/camp2005/

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
June 28--30, 2006, Academia Sinica, Taipei.
URL:
http://www3.stat.sinica.edu.tw/ML/index.htm

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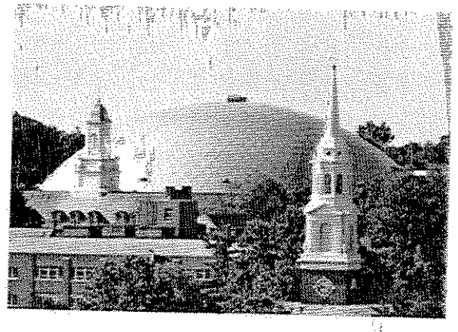
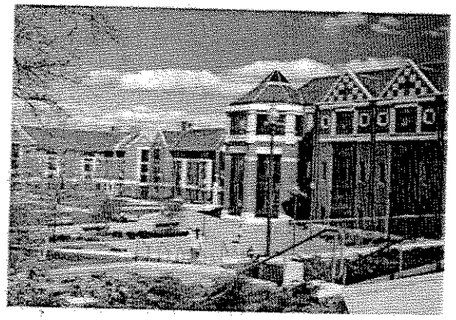
An old gate in ancient Tainan City, Taiwan

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.



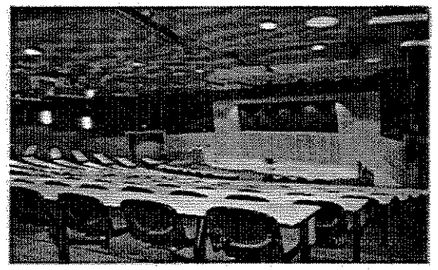


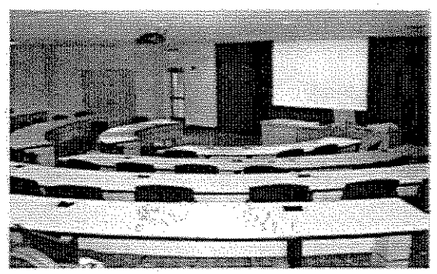
Organized by the International Chinese Statistical Association, this annual statistics symposium will feature three keynote talks by Professors James O. Berger of Duke University and SAMSI, Xiao-Li Meng of Harvard University, and Terrence P. Speed of the University of California at Berkeley and the Walter 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

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: djangf@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.nathanhaleinn.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, Heping Zhang, and Hongyu Zhao.

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

Treasurer and Registrar: Lynn Kuo, lynn@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.q.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: Naitee Ting (chair), naitee.ting@pfizer.com, (860) 732-4871, Fred C. Djang, Lynn Kuo, Ta-Hsin Li, Greg Wei, and Eric Yan.

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

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

International Chinese Statistical Association

泛華統計協會

Membership Application & Renewal Form

Name	(Last)	(Middle)	(First)
(English)			
(Chinese)			
Address			
Office	Address:		
	City:		
	State:	Zip Code:	Country:
	Email:	Telephone:	FAX:
Home	Address:		
	City:		
	State:	Zip Code:	Country:
	Email:	Telephone:	FAX:
Education			
	Degree:	Year Graduated:	
	University:		
Professional Occupation & Title			
	Occupation:	Title:	
Membership Fees			
	Regular (US$40)		
	Student (US$20)		
	Permanent (US$400)		
	Spouse (50%)		
	Donations		
	Total Amount Paid: US$		
Statistical Area of Interest (circle all applicable):			
	A: Agriculture	B: Business / Economics	
	C: Computing / Graphics	D: Education	
	E: Engineering	F: Health Sciences	
	G: Probability	H: Social Sciences	
	I: Biostatistics	N: Theory & Methodology	
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			

International Chinese Statistical Association

January 1, 2005 through June 30, 2005

Profit and Loss

Balance, Dec 2004	**64,625.13**
Income	
2004 interest income (included in 2004 tax filing)	156.90
Membership Dues	1700.00
Total Income	**1856.90**
Expense	
Miscellaneous	
Member dinner at 2004 JSM, Toronto	655.00
Member services	113.94
Total Miscellaneous	768.94
Postage and Delivery	
January Bulletin	1738.90
Total Postage and Delivery	1738.90
Printing and Reproduction	
January Bulletin	2470.00
Total Printing and Reproduction	2470.00
Professional Tax Services	612.25
Total Expense	**5590.09**
Net Ordinary Income	-3733.19
Other Income/Expense	0
Net Other Income	0
Net Income	-3733.19

Balance Sheet

ASSETS	
Checking/Savings	
Checking	30891.94
Savings-Money Market	30000.00
TOTAL ASSETS	**60891.94**
LIABILITIES & EQUITY	
Equity	
Opening Balance Jan 1, 2004	64625.13
Net Income	-3733.19
Total Equity	60891.94
TOTAL LIABILITIES & EQUITY	**60891.94**

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 Hsiao, Chao A. Hsiung, In-Chi Hu, Genshiro Kitagawa, Tze Leung Lai, Wai-Keung Li, Bent Nielsen, Benedikt M Pötscher, Jorma Rissanen, George Tiao, Ruey S. Tsay, Chien-Fu Jeff Wu, Zhiliang Ying, Cun-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 mathe´matiques de Montre´al (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. .

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 7:15pm on August 10th. The buses will board the passengers right after the annual ICSA meeting at 6:30pm 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.

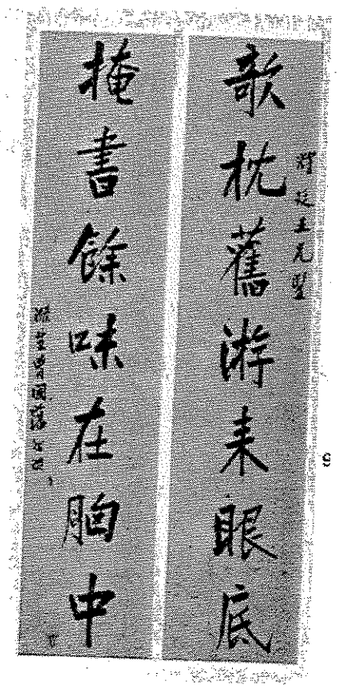
Our Sincere Thanks!
The Editorial Team

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 unforgetable afternoon in our memory.

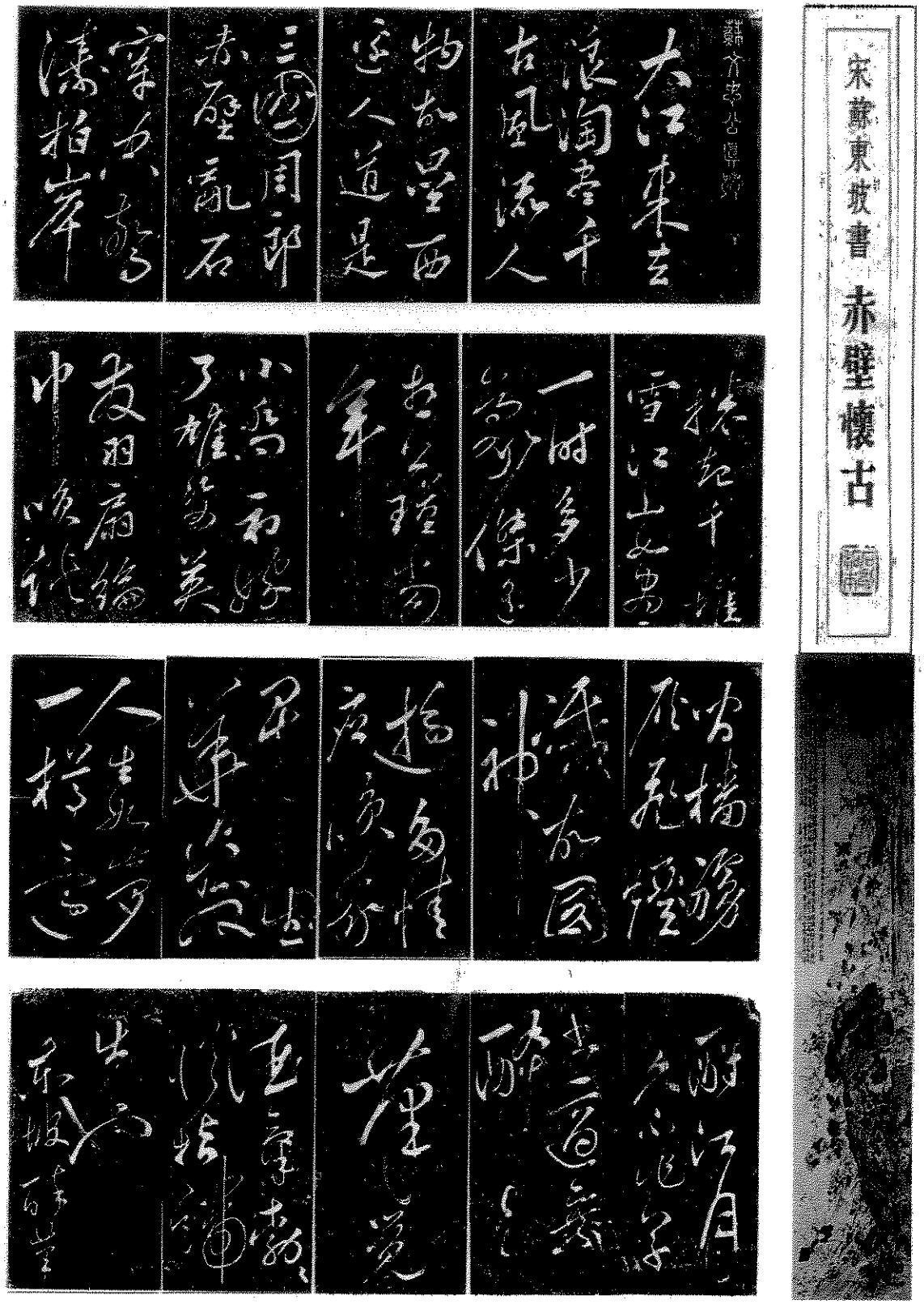
We would also like to thank Professor Fan of Princeton University of his article about financial econometrics. This is both a highly interesting and challenging area of research. In addition, lots of the statistical methodologies can find its applications in this fascinating field.

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.


宋蘇東坡書 赤壁懷古