International Chinese Statistical Association

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Bulletin

會刊

January 2006

Features:

Statistics Without Borders

Interview with a Distinguished Statistician

Overview of Bridging Evaluations in Taiwan

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From the Editor-in-Chief
Tzu-Cheg Kao

I would like to thank our Editorial Members for helping me in many ways in order to publish our Bulletin. Special thanks to the executive members (Yi Tsong, Jiahua Chen, Jun Shao, Ivan Chan, and Weiying Yuan) for continuing support, Kao-Tai Tsai (the past Editor-in-Chief) and Sue-Jane Wang for encouragement and assistance, and Cynthia Liu for preparing the reports and articles for publication.

Some highlights: A special invitation article on *Statistics Without Borders* by the 100th ASA President Fritz Scheuren; an interview with Professor Xiao-Li Meng by Vanja M. Dukic; a special feature article on *Overview of Bridging Evaluations in Taiwan* by Chin-Fu Hsiao et al.; two articles on adaptive design, organized by Jun Shao (the Special Editor of Contemporary Statistical Issues), and information about the 2006 Applied Statistics Symposium by Naitee Ting. In the new submission guideline (detailed in this issue), please note the deadlines are June 1, and December 1 for the upcoming July, and January issues.

My vision for the ICSA bulletin is to serve our members in the best possible way. In order to better serve our members, we really need volunteers for:

- Organizing the topics of general interests of our members
- Interviewing with distinguished statisticians in academia, industry and government
- Serving new, and junior statisticians
- Sharing professional accomplishments, member news, and success stories
- Listing upcoming meeting events
- Reviewing articles and reports

If you are interested in serving ICSA Bulletin as a volunteer or have any suggestions, please contact me as soon as possible.
Thanks for reading this,

Tzu-Cheg Kao

Tzu-Cheg Kao
Editor-in Chief, International Chinese Statistical Association (ICSA) Bulletin
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Editorial Members of ICSA Bulletin

Tzu-Cheg Kao (Editor-in-Chief), Yi Tsong, Jiahua Chen, Ivan Chan, Weiying Yuan, Jun Shao (Special Topic Editor), Cynthia Liu (manuscript format organizer), Jing Xu (Advertising Manager), Kan Wu (cover designer)

Advisors of ICSA Bulletin: Kao-Tai Tsai, Sue-Jane Wang

Executives and Members of the Committees ICSA, 2006

Executives

President:	Yi Tsong (2006)
Past President:	Jiahua Chen (2006)
President-elect:	Jun Shao (2006)
Executive director:	Ivan Chan (2004-06)
Treasurer:	Weiying Yuan (2004-06)

Board of Directors

Greg Wei (Biometrics Section Representative, 2006),
Xihong Lin (2004-06), Ming-Hui Chen (2004-06), Jiqian Fang (2004-06),
Qiwei Yao (2004-06), Hongyu Zhao (2004-06),
Chin-Fu Hsiao (2005-2007), Jian Huang (2005-2007), Jack, J. Lee (2005-2007),
Guanghan Liu (2005-2007), Naisyin Wang (2005-2007), Lixing Zhu (2005-2007),
Josh (Yonghua) Chen (2006-2008), Milton Chung-Lien Fan (2006-2008),
W.K. Li (2006-2008), Peng Li (2006-2008), Suojin Wang (2006-2008),
Mingxiu Hu (2006-2008)

Standing Committees

Program Committee: (Normally 3 years, At most 6 years)
Naitee Ting (Chair 2004-2006)
Yi Tsong (2004-06), Jason Hsu (2004-2006), Xiao-Hua Andrew Zhou (2006-2008),
Wenlian Li (2005-2007), Greg Wei (2005-2007), C.S. Cheng (2005-2007)

Term of reference: To recommend conference and symposium sites, including candidates for their chairs and to recommend general policy for all meetings, subject to approval by the Board of Directors.

2006 Objectives:
(1) 2006 Applied Statistics Symposium will be at University of Connecticut,
(2) 2007 Applied Statistics Symposium will be at North Carolina,
(3) 2007 International Conference will be at Taipei.

Finance Committee
Weiying Yuan (Chair 2004-2006)
H.M. James Hung (2004-06), Yusong Chen (2004-06)

Term of reference: To oversee the budget and to recommend long-term financial planning, including investments of the Association's assets, subject to approval by the Board of Directors.

2005 Objectives: (1) Produce account summary twice a year, (2) Execute T&E approved by the President or Board.

Nomination and Election Committee
Xuming He (Chair 2005-2006)
Gordan Lan (Chair 2004, member 2004-05), Colin Wu (2004-05), Sue-Jane Wang (2004-2006), Kai Ng (2004-2006,kaing@hku.hk), Feifang Hu (2004-2006, fh6e@virginia.edu)

Term of reference: To nominate the candidates for President-elect and members of the Board of Directors.

2005 Objective: Produce ballot and complete election prior to ASA/JSM in August.

Publication Committee
Jun Shao (Chair 2005)
Kao-Tai Tsai (Bulletin), Hwai-Chung Ho (Statistica Sinica), Jang-Ling Wang (Statistica Sinica), Ivan Chan (ex-officio), Zehua Chen (2005-2007: stachenz@nus.edu.sg), Jianguo (Tony) Sun (2005-2007: tsun@stat.missouri.edu)

Term of reference: To oversee the publication policy of the Association and make recommendations to the Board of Directors.

2005 Objectives:
(1) Coordinate the selection of new editors for Statistica Sinica.
(2) Discuss possibility of e-journal possibility for Statistica Sinica and ICSA Bulletin.

Constitution Committee
Shein-Chung Chow (Chair)
Chien-Pai Han

Term of reference: To review the Association's Constitution and By-Laws and prepare a revision if necessary.

Current Committees

Membership Committee
Jun Zhao (Chair 2005, member 2003-05)
Qiwei Yao (2003-05, Europe), Rongdean Chen (2004-06), Ming Tan (2004-06), Heping Zhang (2004-06), Gemai Chen (2005-2007, gchen@math.ucalgary.ca), Shu Yan He (2005-2007, shu-yen.y.ho@gsk.com), Shun-Yi Chen (2005-2007 sychen@math.tku.edu.tw), Lixing Zhu (2005-2007, lzhu@hku.hk), Ouhong Wang (2005-2007, WANG_OUHONG@Lilly.com), Wei Shen (2005-2007, SHEN_WEI_X1@Lilly.com)

Term of reference: To recruit new members and contact interested potential individuals and organizations.

2005 Objective: Try to work with applied symposium, JSM, and other opportunities to recruit new members.

Awards Committee
Jianping Dong (Chair 2005)
Wen-Jang Huang (2004-06), Zhaohai Li (2004-06), Jane-Ling Wang (2004-06), Lingshi Tan (2005-2007), Hanfeng Chen (2005-2007), Gang Zheng (2005-2007)

Term of reference: To accept, evaluate, and recommend nominations for ICSA various awards.

2004 Objectives:
(1) Recommend Service and Achievement Awards candidates to the Board.
(2) Retrieve historical Award recipients' list to be published on the ICSA Web.

Communication Committee
Don Sun (Chair, Web)
Hubert Chen (Listserv), Li-An Xu (2004-2006)

Term of reference: To evaluate the database and use of internet.

Applied Statistics Symposium Committee
Yi Tsong and James Hung (Chairs)

Term of reference: To organize the Applied Statistics Symposium, 2005, in Washington DC.

Book and Journal Donation Committee
Tar Timothy Chen (Chair)

Term of reference: To solicit book and journal donations and to arrange their delivery to universities or colleges in need.

Annual Meeting Committee
Wenlian Li (Chair 2005, member 2004-2005)

Term of reference: To plan, coordinate, and arrange the August annual meeting, 2005.

Archive Committee
Ivan Chan (Chair 2005)
Smiley Cheng, Shein-Chung Chow, Nancy Lo, Naitee Ting

Term of reference: To plan and implement electronic archive for the Association.

Strategic Committee
Frank Shen (Chair 2005)
Zhiliang Ying, William W.S. Wei, Chao Agnes Hsiung, Chien-Pai Han, Tar Timothy Chen, Jeff C. F. Wu, Shein-Chung Chow, Kuang-Fu Cheng, Smiley Cheng, Chiao Yeh, Yuan A, Chow, Jack C. Lee, Grace Yang, Jia-Yeong Tsay, James Fu, George Tiao

Term of reference: To plan long-term strategies for the Association.

Biometrics Section (2005)

Naitee Ting (Chair)
Sue Jane Wang (Former Chair), Jen-Pei Liu (past Chair), Shou-en Lu (secretary), Gang Li (treasurer), Wayne Weng (ICSA Representative 2003-05)

LETTER FROM THE CURRENT PRESIDENT

Yi Tsong, Ph.D.

Dear friends:

Happy New Year! With the effort of our Ex-President Jiahua Chen, Officers, Board of Directors, Committees and support from all of you, our organization enjoyed another glorious chapter in 2005. I would like to take this opportunity to thank you all for your supports to ICSA. I am looking forward to work with all of you to make the most of this association. Now, we are opening the New Year 2006 under the new management crew including Editor-in-Chief of ICSA Bulletin Tzu-Cheg Kao. We regret to see the departure of our President Jiahua Chen and Editor-in-Chief of ICSA Bulletin, Kao-Tai Tsai. Under President Jiahau's direction, a thorough research on the web improvement was conducted in order to improve the function and service of our website. A research committee was also formed which is chaired by Naitee Ting to study the needs of an applied statistical journal. During his 3-year tour of duty, Kao-Tai and his editorial team transformed the ICSA Bulletin into a lively journal with a series of classical Chinese paintings. It became a collector's item now. Now it is time for Tzu-Cheg to show his tricks. In this issue, he certainly opened your eyes wide again.

I am very fortunate to have the opportunity to serve on the staff of President Chen in 2005. With this valuable experience, I will continue my service as the president of ICSA in year 2006. We have a plenty to looking for in 2006. First, the search for the website vender and designer will be complete and move on to design and production stage soon. With this, ICSA may create a few online services such as statistical forum, online election voting, membership payment on line and conference/symposium registration etc. Second, we will be able to decide the feasibility of an applied statistical journal of our own. With this, statistical articles of applications in the fields most relevant to the professional lives of ICSA members will be collected and published. Third, we will have an ICSA Bulletin with new revised design and content. As you may see that some changes were already taken place to satisfy the needs of the readership. Actually, with all the effort that the management staff there is always some specific services that are missed. Your voices on it need to be heard.

Finally, please remember to take time to visit ICSA web site frequently. You will find much timely and important information posted there.

Hope you have a Grand New Year!

Sincerely yours,
Yi Tsong, 301-796-1013, email TSONG@CDER.FDA.GOV

Message from the Past President

Jiahua Chen, Ph.D.

The year 2005 has been both a very long and very short year. It was a fast-forward year from a president-in-training to very soon a past-president for me. Yet, with the overwhelm support of our members, the International Chinese Statistical Associate has filled the past year with many activities and successes.

The annual event of the ICSA Applied Statistical Symposium attracted over 180 participates. The meeting was held from June 12-15, 2005 at Washington DC Metropolitan Area. The symposium contained well diversified and yet focused programs in the form of statistical workshops, invited and contributed sessions. The participants enjoyed the outstanding academic programs as well as had a great time during our traditional banquet with great Karaoke entertainment.

Another bright point of the year should be attributed to the annual banquet organized by Professor Wenlian Li and his local committee during the Joint Statistical Meeting. For the first time in the history of ICSA, over 400 delegates joined us for the event and cruised on the beautiful Mississippi River. The booth of ICSA was surrounded constantly by participates from all stripes. The event contributed substantially to the popularity the ICSA and will no doubt have a very strong positive effect to our membership recruitment.

The membership of any associations is a permanent issue. We have been very successful at attracting new members through the Applied Statistical Symposium, and the activities during the Joint Statistical Meeting. Each year, a large number of new members joined the ICSA through these two avenues. This year, the ICSA has signed agreement with the ASA for the special rate membership. We enthusiastically urge our members to take this advantage and join one of the most prominent statistical associations. With a significance presence of the ICSA members in ASA and other major statistical societies, the profile of the ICSA will be further highlighted. Actively recruiting members from Mainland China has been another focus of the ICSA membership committee. Due to a variety of reasons, the progress in this direction is mild. I would like to appeal to our current members to encourage your friends and connections in China to join the ICSA. One concrete contribution you can make is to identify and recommend potential candidates who have more flexibility at traveling from the Mainland China to join the board of the ICSA.

Under the leadership of our nomination chair, Professor Xumin He, the election in year 2005 had been a big success. The election results were announced during the Joint Statistical Meeting and have been posted on the ICSA website. In particular, Professor Jun Shao from the University of Wisconsin-Madison is now the president-elected, following Dr. Yi Tsong who is going to serve as the president of the ICSA in the year 2006. At the beginning of each year, the new president recruits members for various committees and

committee chairs. Thus, it is the right time now for you to think about volunteering your precious time for the benefit of the ICSA. At the same time, the ICSA constantly looks for new blood to join the board. The search for candidates of new president will also start very soon. The ICSA has a large pool of talents. Without your active participation, we may not be able to fully utilize it. Whether you hope to serve in committees or as a board member of the ICSA, the door is widely open. Please make your willingness noticed by our nomination committee and/or the incoming president, Dr. Yi Tsong at your earliest convenience.

The ICSA members play a big role in statistical research, application and in serving the statistical community at large. Their contributions are recognized in various capacities. Most noticeably, the editorial boards of all major statistical journals have a strong presence of the ICSA members. More and more ICSA members participated in committee works of other major statistical organizations. Some have successfully been elected to the position of presidency and many more are being nominated. There is no doubt that the ICSA members will appear more and more often in the election ballets of major statistical associations. I would strongly urge our members to exercise their precious right when it comes to vote for your favorite candidates in the associations you are also a member.

Reluctantly and sadly, I must also share some sorrow news with you. The ICSA lost two of its most influential statisticians and permanent members, Professors Xiru Chen (1934-2005) and Ping Cheng (1932-2005) in the past year. Professor Xiru Chen was the only fellow of Academia Sinica (China) in statistics. He was most renowned for his contributions in large sample theory in parametric and nonparametric statistics. He is widely regarded as one of the scientists who revitalized the statistical research in the Mainland China after the Cultural Revolution. Professor Ping Cheng retired in 1997 from the Institute of Systems Science after serving as its head for many years (1983-1995). He had been troubled with a number of chronic diseases. He was best known for his significant contributions in the reliability analysis of complex systems of practical importance. He made substantial research contributions on asymptotic efficiency, admissibility of point estimation and other areas of mathematical statistics. In a more personal note, I obtained master's degree under the supervision of Professor Ping Cheng on the topic of Bahadur's efficiency of the maximum likelihood estimators. As recently as at beginning of the year 2005, I had the honor to present a talk at the University of Science and Technology of China at the presence of Professors Xiru Chen.

I found myself very fortunate to have the opportunity to direct interact with many of the best minds in statistics. It has also been the greatest honor to serve the ICSA in the capacity of president in the past year. My sincere thinks to go all of you whose supports are the most wonderful gifts I received!

Jiahua Chen, University of Waterloo, Ontario, Canada

From the Executive Director, ICSA

Ivan S. F. Chan, Ph.D.

On behalf of ICSA, I would like thank all of you for your generous support for the various ICSA activities in 2005. In June, we held the Applied Statistics Symposium in Bethesda, Maryland, which attracted more than 200 attendees. It was a very successful symposium in terms of both quality and variety of topics discussed. In addition, the banquet with Karaoke provided a great opportunity for participants to network, relax, and entertain. At the annual JSM banquet event in August, we had our first-ever ICSA dinner cruise on the beautiful Mississippi river. According the Wenlian Li (Chair of the local committee), the dinner cruise attracted more than 400 people, including many non-ICSA members. This is really a tribute to the incredible efforts of the local committee, which also made the ICSA booth one of the hot spots at the JSM registration area. This year we also held two very productive board meetings where many important issues concerning the operation and future development of ICSA were discussed. We thank Jiahua Chen (President) for his leadership, and we also thank the board members for their generous support.

This year we elected several ICSA officers: 2006 President-elect and 6 members of the Board of Directors for 2006-2008. Election ballots were sent to all members via email (or mail if no valid email address is available). Members were encouraged to return their votes by email. Similar to last year's process, votes were counted by computer programs that were developed and validated by an independent team of 3 volunteers: Drs. Jacksen Lou, Joshua Chen, and Bill Wang. As part of the vote count, a statistical sampling-based QC check was performed to ensure the accuracy of the vote count. The results (see Table 1 below) have been announced at the Members Meeting at the JSM in Minneapolis and on the ICSA web. I would like to express my sincere thanks to all of the candidates for their enthusiasm and support of ICSA, to the nomination committee for their great coordination, and to the volunteer team for helping with the electronic vote count. I would also like to congratulate and welcome the newly elected President-Elect (Professor Jun Shao) and 6 board members. As a separate note, there are 6 board members whose term ended in 2005 (Jiahua Chen, Greg Wei, Frank Shen, Ivan Chan, Xuming He, and Shu-Yen Ho). We thank them for their tireless efforts and generous support over the past 3 year, serving on the ICSA board.

As we continue to update our membership database, 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).

Best wishes to all of you in 2006.

Ivan S. F. Chan
Executive Director, ICSA

Ivan S. F. Chan, Ph.D. is Director of Clinical Biostatistics, Biostatistics and Research Decision Sciences, Merck Research Laboratories, and he can be reached by sending him an e-mail to Ivan_Chan@Merck.Com

Results of 2005 International Chinese Statistical Association (ICSA) Election Based on Votes from 107 Members August 3, 2005

ICSA Office	Candidate	Number of Votes	Elected
2006 President-elect	SHAO, Jun (University of Wisconsin)	54	X
	WANG, Sue-Jane (FDA)	50	
Directors of ICSA Board (2006-2008) (6 directors to be elected)	CHEN, Yonghua (Josh) (Merck)	52	X
	CHEUNG, Siu Hung (The Chinese Univ. of Hong Kong)	35	
	FAN, Milton Chung-lien (FDA)	51	X
	LI, W.K. (Univeristy of Hong Kong)	59	X
	LOU, W.Y. Wendy (University of Toronto)	44	
	LI, Bing (Penn State University)	53	X
	SHAO, Qi-Man (Hong Kong Univ. of Science and Technology)	37	
	SONG, Peter Xue-Kun (University of Waterloo)	36	
	WANG, Suojin (Texas A&M U)	57	X
	HU, Mingxiu (Pfizer)	52	X

An Extraordinary Turn Out On The 2005 JSM Banquet

Naitee Ting, Ph.D.

As you may be aware of, the ICSA has a tradition that on the Wednesday evening of each JSM, there is an ICSA dinner banquet. The 2005 JSM took place at Minneapolis, MN, and Professor William Li of University of Minnesota led the effort to prepare for this event and they made it a great success. The banquet took place on a cruise ship and there were over 250 people participated. Every one had a good time and enjoyed both the dinner and the Mississippi river view.

Professor Li started the planning over a year ago. He was approached by the ICSA Program Committee earlier in 2004, and was requested to help organizing the 2005 ICSA banquet during JSM. Professor Li organized a local committee to plan for this event. In spring of 2005, the committee decided to have the banquet on a cruise boat that will be traveling on the Mississippi river during the event. In order to make this arrangement, the committee worked hard to negotiate a reasonable price with the boat company - there were many expenses involved (bus from convention center to the boat and back, charge for cruise, and charge for dinner). The final deal the committee made with the boat company enabled the ICSA to set an attractive ticket price and made this cruise possible.

During the JSM, committee members and students worked very hard to promote this banquet. We have many local professors, statistical professionals and student helpers. By Wednesday evening, all the hard work paid off and the banquet turned out to be a very successful event.

On behalf of the Program Committee, I would like to express our sincere appreciation of Professor Li and the local committee, for their great effort, their thoughts and their hard work. Local committee members include Tiefeng Jiang, Na Li, William Li, Wei Pan, and Baolin Wu. In addition, there were 11 student volunteers: Qin Cao, Hua Dong, Yi He, Meijun Li, Haiying Lin, Wei Liu, Fujin Lu, Yiqun Mou, Huixin Wang, Lifeng Wang, and Peng Wei.

In the past, number of participants of the ICSA banquet at JSM has never exceeded 200. Professor Li and the local committee certainly broke this record.

Let us take this opportunity to thank Professor Li, the committee members, student helpers, and all of the volunteers who helped making this success.

Naitee Ting, Chair, Program Committee, ICSA

Statistica Sinica: New Face and New Scope

Michelle Liou and Xiao-Li Meng

The first issue of Volume 16 (2006) of *Statistica Sinica* features a new "Ying-Yang" cover design. The outward "Yang" design on the front cover represents dissemination of wisdom, and the inward "Ying" design on the back cover symbolizes absorption of knowledge. The back cover also highlights the new scope of Statistica Sinica:

"*Statistica Sinica endeavors to meet the needs of statisticians faced with a rapidly changing world. It publishes significant and original statistical articles that promote the principled use of statistics along with related theory and methods in quantitative studies, essential to modern technologies and sciences. It is published quarterly in January, April, July and October.*"

We therefore invite suggestions and proposals of theme topics that can reflect and highlight this new scope. As an example, see the accompanying call for submissions to the theme topic on "Algebraic Statistics and Computational Biology", a call that can also be found at the *Statistica Sinica*'s web site http://www3.stat.sinica.edu.tw/statistica/. We very much welcome general suggestions and submissions, as well as submissions to this theme topic.

The new issue also debuts a new column: Editor's Mélange. The following are the first couple of paragraphs of our first editorial for this column:

"As the new editors, we are deeply honored to be called upon to guide *Statistica Sinica* through its next scholarly venture. In just 15 years since the first issue appeared in January 1991, *Statistica Sinica* has been built into a viable choice for scholarly publication in statistics. We are indebted to the tremendous efforts of its founding editor, Professor George Tiao, and all of our predecessors. We feel privileged to be trusted to reach out to a new generation of statisticians. At the same time, we feel a weight on our shoulders. Perhaps our feelings can be best related to those of parents of a well brought up youth, who strive to do whatever they can before the end of the teenage years (or of our term), to assist the building of her/his life for many years to come.

Nature holds its own process of selection and evolution. The same applies to journals – the survival of the fittest undoubtedly ensures a better future. Through this editorial, we introduce our plans to more efficiently handle submissions and publish the best and most engaging papers, with an understanding that a journal not only survives on, but also strives for, a reflection of the emerging interests of the authors and readers. Our planned efforts, therefore, focus on higher intellectual standards, faster publication time, and enhanced readability."

We very much hope you will pick up a copy of the new issue of *Statistica Sinica* to find out the rest of our editorial and much more .....

Michelle Liou and Xiao-Li Meng

Statistics Without Borders

Fritz Scheuren
100th ASA President

As President of the American Statistical Association (ASA), I have come to talk today about ways to enhance the cooperative relationships that already exist between the International Chinese Statistical Association (ICSA) and ASA.

To indicate the importance of these needed new relationships, let me talk first about the just started international thrust that ASA has taken under my direction in reaching out to our fellow national statistical associations around the world. Then I will go on to talk of ICSA specifically. And, finally, I will thank you for your attention and invite questions.

ASA's International Thrust

Even though we have only just begun, a brief summary of what ASA has done to date might be in order. We provide this below, then add a few generalizations that we expect to hold up when we have made a complete round featuring each society. Specifically we have in mind questions of size, date of founding, and primary focus. But first some examples:

As I hope you all noticed in the November 2004 issues of AMSTAT NEWS, the International Chinese Statistical Association (ICSA) was featured. This was the first among the many that have followed and indeed continue. ICSA founded at the 1987 Joint Statistical Meetings in San Francisco by a group of Chinese statisticians led by Professor George Tiao from the University of Chicago. Since then, its membership has grown close to 1,500, including members from all over the world. Although the society has a strong Chinese cultural base, it has many non-Chinese members and continues to welcome non-Chinese statisticians. I am a member, for example, and have been since about 1997.

In December ASA featured the Inter-American Statistical Institute (IASI). Based in Panama and Argentina, IASI was founded in 1940 with the purpose of promoting the development of statistics in the American region. The IASI is a nongovernmental organization with institutional and individual members, IASI is affiliated to the International Statistical Institute (ISI) and has consultative status with the United Nations Economic and Social Council.

The January issue of Amstat saw the Spanish Society of Statistics and Operations Research featured. It was created on February 12, 1962, with the name "Sociedad de Estadística e Investigación Operativa" (SEIO). Since then SEIO has grown to about 750 individual members. The purpose of SEIO is to develop, foster, and disseminate statistical and operations research knowledge, methodology, and good practice.

Next in the February issue, Amstat featured the Associação Brasileira de Estatística (ABE), founded in 1984. The ABE promotes the development, dissemination, and application of statistics in Brazil. It grew out of the need to provide structure for statistical activities that were already taking place and, in particular, to provide a more permanent basis for organizing the SINAPE (Simpósio Nacional de Probabilidade e Estatística), the biannual meetings that started 10 years earlier.

With the March issue of Amstat there was a report from the Portuguese Statistical Society (SPE). The SPE was founded in 1980; and, hence is celebrating its 25th anniversary this year. The society has approximately 750 individual members. These individuals come from universities, schools, businesses, public administration, and information agencies, as well as several institutional members, representing these various sectors of society.

In April the Statistical Society of Australia, Inc., (SSAI) was featured in Amstat. Formally established in 1962 as a national organization for Australian statisticians, SSAI acts as an umbrella organization for six state branches and members scattered around the world. Currently, membership stands about 800. The origins of the society date back to 1947 when the Statistical Society of New South Wales was formed. Initially there was very little interest in forming a national body because very few statisticians worked outside Sydney and Melbourne. Formation of the Canberra Statistical Society in 1961 by a group led by P.A.P. Moran was the catalyst for the formation of the national body. Other branches to join were Western Australia in 1964, Victoria in 1965, South Australia in 1967, and Queensland in 1981.

The Argentinean Statistical Society (SAE), featured in the May Amstat is a technical and scientific nonprofit organization that aims to promote the development of statistics in Argentina. The organization was created on July 13, 1952, at the first Statistical Colloquium organized by Professor Fausto I. Toranzos at the National University of Cuyo. The SAE is formed of representatives from various regions of the country, a characteristic that allows it to meet all the needs of its members.

Maybe that is enough to give you a flavor. But for the sake of completeness, in June AMSTAT featured the Irish Statistical Society, followed in my particular order by the National Societies of Finland, Korea, Canada, Mexico, Ethiopia, among others. Anyway, when done, we will hope to have introductory articles from most professional statistical societies and from every continent.

Some Generalizations

Most statistical societies are relatively recent in origin—certainly those listed above are. Around World War II or in the decade or so afterwards there was a watershed for many countries with statistical societies being founded about that time. Some of the European

societies, though, were started many years earlier—the Royal Statistical Society (RSS) being perhaps the oldest. RSS was founded, as was ASA, in the 1830's and indeed is slightly older than ASA.

All of the societies are modest in size (generally under 1500 members), as compared to ASA. RSS again, though, at 6000 is an exception. But this comparison to ASA is generally true only in terms of absolute numbers. And absolute size is not a good measure. Many of the societies (including the RSS), if we were to do the calculations, have higher membership rates relative to the populations of their country of origin, than is the case with ASA.

All of the societies have one or more journals, offer regular meetings and seek to make a positive difference in the use of statistics in their home countries.

Most journals interestingly appear in English. Few, as yet, are available electronically, although this is coming. Offering free electronic access to journals, as a right of membership, is rare indeed. As far as I know, ASA may be the only national statistical association that does this now and we just started this year (2005).

By now it should be clear, if it was not already that statistics is truly a profession without borders. To anchor this point a web book is planned by ASA eventually, for easy reference.

International Statistical Chinese Association

It goes without saying that ASA has a lot to learn from other national societies, if we are to continue to grow more responsive to our members and the citizens of whatever country we are from. This statement is particularly true of ICSA, which is thriving.

ICSA, by all measures is a great success and ASA needs to examine why. Strong in theoretical and applied scholarship, camaraderie, still having a personal touch, and already well represented in many applied niches (in Biopharmaceutical statistics, for example). In less than 20 years ICSA has risen to be the third largest statistical society in the world. A great achievement!

ASA's International Membership Initiatives

ASA has begun several forms of international outreach. Three might be mentioned. The first two of which have been undertaken for developing countries:

First, for the developing world we are rejuvenating a form of ASA membership that provides access to our journals electronically at a reduced rate, as part of membership (under half of the rate paid by everyone else.)

Second, in partnership with the Educational Testing Service, ASA is sponsoring an initiative that would help defray the cost of admission tests to American universities for persons applying from developing countries. Such individuals would be offered free student membership during their US graduate school years.

Third, and perhaps of most interest, ASA is offering a $10 discount for members of national professional statistical societies who join ASA. The reduced ASA rate is a unilateral offer and all that is asked is that each participating national statistical society make their members aware of the new program. Incidentally, for those who worry about such things, the joint membership offer is expected to be close to cost neutral. **ICSA in the first test case and its members have been the first to benefit.**

Some Concluding Remarks

ASA, as an American institution, by its nature has to be filled with members who have roots everywhere. Now, despite the myth of the melting pot, we do not lose these roots, even generations later. Some of us, including me, are members of several national statistical societies, in addition to ASA. In my case, I am a member of the Statistical Society of Canada, the country my mother's family came from, and, also the International Chinese Statistical Association, the country of my wife's birth. While I initially joined these societies to show solidarity, I stayed because of the deep scholarship I found there that aids me in my practice.

Bottom line here, I believe that these changes by ASA, in some cases inspired by ICSA, will add measurably to the sense of community we all should have as statisticians, no matter what our country of origin. The changes are part of a respect/respect relationship, so central to the harmony that science is built on.

Acknowledgments and a Clarification

The outreach to national professional societies was an idea that Brad Efron had and that I helped structure and implement. Martha Aliaga of the ASA Office, the former and current international ASA board members, and the ASA Committee on International Relations have all made considerable inputs. The role of Monica Clark, also of the ASA Office, in paralleling, for local ASA chapters, a similar program is also to be commended.

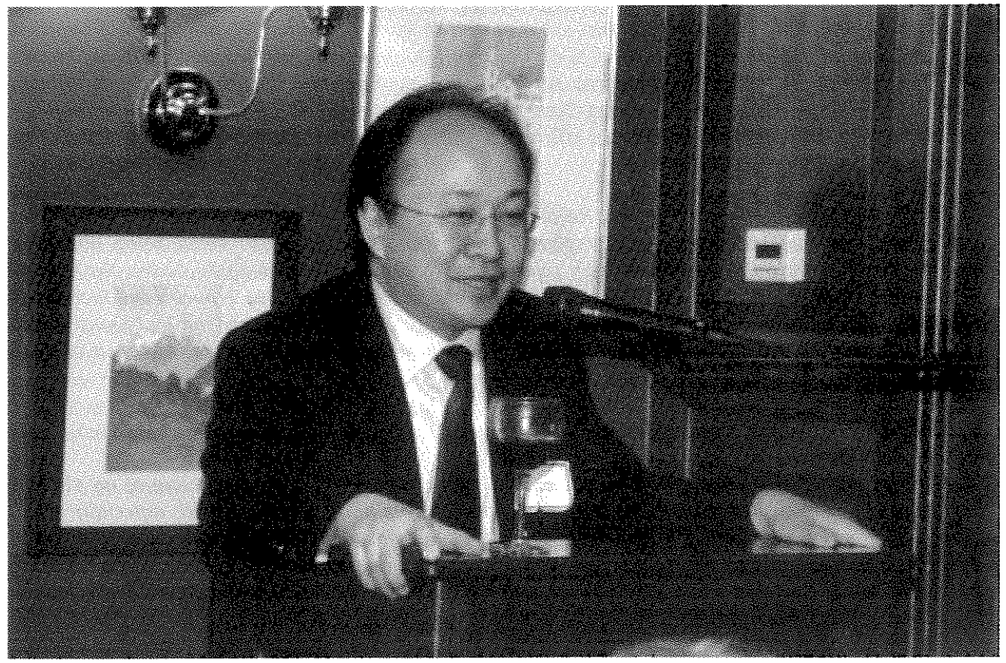
Clarification—On its face it would seem that I have given myself a $10 dues reduction, since I belong to several national societies besides ASA. This turns out not to be true as I am a life member of ASA (and now that's to your generosity, also of ICSA). Incidentally, the 10% reduction is only available once—no matter how many national statistical societies a person belongs too.

Interview with a Distinguished Scholar

A Conversation with Professor Xiao-Li Meng

By Vanja M. Dukic, University of Chicago[1]

Abstract. Xiao-Li Meng was born on January 24, 1963, in Shanghai, China. After obtaining his undergraduate degree from Fudan University in Shanghai, he taught mathematics at China Textile University for two years, before returning to Fudan for his master study in mathematical statistics. He joined Harvard University in 1986, where he obtained a PhD in Statistics in 1990, working with Don Rubin on the EM algorithm and multiple imputation and with Professor Shaw-Hua Lo on survival analyses and asymptotics. Professor Meng was on the faculty of the University of Chicago for ten years, and in the year 2001 he returned to Harvard, where he is now the chairman of the Statistics Department. Professor Meng is the 2001 COPSS winner, recipient of the 2003 ICSA Distinguish Achievement Award, fellow of ASA and IMS, Co-editor of *Statistica Sinica*, member of numerous editorial boards, and is currently nominated for 2007-2009 vice-president of the American Statistical Association. He has over 70 publications, and continues to spread his passion for statistics wherever he goes.



Xiao-Li Meng, Speaking at Art Dempster's Retirement Party, May 20, 2005.

[1]With special thanks to Dr. Radu Craiu (University of Toronto) and Dr. Lei Sun (University of Toronto) for their kind hospitality and helpful comments and suggestions while working on this article.

Introduction

How best to introduce Prof. Meng? When I was asked to conduct this interview the first thing that came to mind was "how many pages do we have?" It turned out, fortunately, that the answer was "as many as we wished to fill." Although I cannot really say that I accomplished that goal – as there are many more stories about Prof. Meng that would have to wait for another occasion and even more space -- I can only hope that the space filled can give you a glimpse of Prof. Meng's professional achievements, as well as his extraordinarily generous and well-loved personal side. It is a collection of conversations and interviews, held with friends over many dinners and bottles of wine, and a few of the stories which colleagues of Prof. Meng have shared with us.

A Professor of Words and Numbers

VMD: Not only are you one of the most highly cited researchers in the mathematical sciences (you were ranked among top 25 by the Science Watch among all articles published and cited between 1991 and 2000), but you also have quite a number of memorable funny quotes attributed to you. I remember you at one of the ENAR meetings shortly after becoming the chair at Harvard, responding to people that "a great perk for being a chair is that I now can do *search* whenever I cannot do *research*". Or, "It's all missing data to me!" (Prof. Meng has also been caught saying on occasion to his students and post-docs that "Latex is good for soul", but somehow that did not catch on as much.) Similarly, many of your papers do not seem to have a "normal" title – there is always a pun, some word game, a funny analogy: "Missing Data: Dial M for???", "The EM Algorithm: An Old Folk Song Sung to a Fast New Tune", or "Meeting Hausdorff in Monte Carlo: A Surprising Tour with Antihype Fractals". Your fondness for words is remarkable – in fact, you have an unusual affinity for both numbers and for words. Can you tell us more about that?

XLM: *Yes, in China during the Cultural Revolution, almost all parents wanted their children to learn a certain skill, such as painting or calligraphy for example. It was a way to avoid being sent to the countryside after finishing middle or high schools (universities were shut down during the Cultural Revolution). I spent most of my time doing calligraphy, and was very interested in poetry and literature in general. But I was also always very interested in mathematics – in fact, it turned out that I was lucky to have a couple of very good middle-school teachers in mathematics who instilled the love for it in me. So poetry, literature, and math have always played a great part in my life.*

VMD: Were your parents supportive?

XLM: *Both my parents were school teachers, so they were naturally very supportive of my study. In particular, my mother, like many Chinese parents then (or even now), was very strict, especially when it came to matters of education. She had a number of ways to punish me if I did not do my best in school. Well, I will not give any details here as I don't think any of these methods is acceptable in this country. But I have to say that they worked well on me, and as I grow older I am becoming more appreciative of my mother's effort and intention ...*

From calligraphy to math to stats

VMD: So when did you realize that you are very good at math?

XLM: *It was when the Cultural Revolution ended and the whole country had a "math fever" because of a glorifying newspaper article on how a Chinese mathematician, Jing-Run Chen, obtained the closest result*

to the "Goldbach Conjecture"[2], which, as far as I am aware, is still open. Ironically, Chen's achievement was partially due to the Cultural Revolution because he couldn't do anything else but to bury himself, literally, in layers of scratch papers for years. So there were plenty of intriguing math-competition type of problems around, and somehow I gained a reputation, in my middle school, as being the one who could solve all the problems. Of course, no one could solve all the problems, but I was able to solve a bit more than my classmates. I was then sent to try a pre-test for taking the national college entry exam – I had to take the pre-test because the entry exam required a formal high school education, which I did not have. The pre-test consisted of only math and literature, which was particularly good for me because both were my strong subjects. I ended up ranking number two on either test but number one in the combined score in my county, gaining the permission to take the national college entry examination – or I should say the entry point of my professional career.

VMD: Then after getting your theoretical mathematics degree from Fudan, you got a job at China Textile University in Shanghai teaching mathematics. What was the path that led you into statistics?

XLM: *Yes, I taught for a couple of years there, before being given an opportunity to go back to Fudan for a master program in mathematical statistics. I took every course in probability and stochastic processes I could at Fudan – they were very theoretical, but they had many courses in that field. They fascinated me.*

VMD: What was the reason that made you transition from mathematics to statistics?

XLM: *After taking all seven courses in stochastic processes, I was really fascinated by the idea that one can use <u>precise</u> mathematics to describe <u>random</u> phenomena occurring in real world. This fact still fascinates me, and likely will for the rest of my life. So studying statistics became my destination.*

The Harvard Years

VMD: So after finishing your master study at Fudan in 1986, you applied to Harvard for your doctorate. How did you choose Harvard?

XLM: *Actually, I took an advice of a classmate, who just got into Purdue Statistics, that I should apply to some big, some small, and some medium schools. So I chose Harvard as one of the big ones, and everyone laughed at me... I was one of the very few (then) Chinese students to even apply there. I also applied to Berkeley, Purdue, Wisconsin, Ohio State, Pittsburgh and Bowling Green State. I was admitted to all of them except for Berkeley, which still has not sent me their decision ... (Laughter.)*

VMD: You wrote an interesting application, right?

XLM: *Yes, I chose Empirical Bayes as the central theme for my personal statement. Wait – it just occurred to me that might be the reason that my application was tossed out by the Big B! (Laughter.) It had a bit of the tone of "Mao's wisdom." In those days we typically started a paper or chapter with a quotation from Mao, and then built it somehow into the paper. It was said and believed then in some Chinese statistical circles that Bayesian statistics was banned then because of a quotation due to Mao implying that prior knowledge can never be trusted. I therefore discussed in my statement that the fact*

[2] The original Goldbach's conjecture was first written in his 1742 letter to Euler, stating that "at least it seems that every number that is greater than 2 is the sum of three primes." Euler then proposed an equivalent form (now commonly referred to as the Goldbach conjecture) stating that "all positive even integers greater than 3 can be expressed as the sum of two prime numbers." In 1978 Chen showed that all sufficiently large even numbers can be written as the sum of a prime and the product of at most two primes, the so-called "1+2 result".

that Empirical Bayes uses data to estimate the prior may make it easier to be allowed in China. But I have to confess that I really did not know much about empirical Bayes then, and I still do not fully understand it now! Nevertheless, Don Rubin later told me that I was admitted partially because of that statement, for Don said that it was somewhat unexpected that I did not brag about my mathematical ability, as mathematical applicants often do, but rather tried to make some sense out of a statistical concept.

VMD: How were your years at Harvard?

XLM: *When I first came to Harvard, I thought I knew much about statistics, after having taken so many math and stochastic processes classes... Soon I'd learn how naïve I was! For my first year, I followed the common wisdom to take some hard and some easy courses to "balance things out". The only problem was that I got completely wrong what's easy and what's hard! For example, I thought applied regression would be just about taking derivatives and finding least squares estimates, which I have done many times before. But... they started looking at residuals, then transforming variables, even on both sides, then fiddling with the residuals again, and then making more transformations—I was simply lost for I didn't know where to stop or how to stop! (Sadly, I still don't!) My whole semester was essentially taken up by that one single "easy" course! In addition, I never even saw a histogram or stem-leaf plot before coming to Harvard. I still recall Don's puzzling expression when I asked him about a stem-leaf plot ...*

Speaking of puzzlement, I still recall that the first time I sat in Don's data analysis seminar course, he was talking about U.S. census. I was so puzzled. What is so hard about counting people that it would need a Harvard professor to lecture on it? Although I hesitated to speak then because of my very poor English, I couldn't conceal my puzzlement – I raised my hand: "Prof. Rubin, in China, the counting is easy -- everybody has a number!" Don looked at me and then announced to the rest of the class: "Xiao-Li is very innocent!" Thankfully, Shaw-Hua, who also sat in, came to my rescue: "Oh, Don, I know what Xiao-Li means – in Taiwan it is even easier – we have a curfew!" I guess you can see now how little real-life statistics I knew then ...

Time for everything

You have a very distinguished career in the statistics field: you won the COPSS Award in 2001, you are the co-editor of *Statistica Sinica*, the chairman of the Statistics Department at Harvard, and now a candidate for the vice-presidency of the ASA. You have also mentored sixteen doctorate students and two post-docs, all of who admire your dedication and selflessness when it comes to spending time with them. You have authored over 70 papers, and have collaborators all over the world. My first question: how do you find the time to do all these things and do them well?

XLM: *Well, time is a relative concept, especially when the boundary between work and leisure time is a blurred one. For example, I often take reviewing articles as my "relaxing time" for I enjoy learning what others are doing. If I have any secret for finding time, it is that I am very efficient in bed—the moment I hit the pillow, I am gone! (Laughter.) I also love doing research while on the road – airplanes and hotels are really ideal environments for deep thoughts for there is little distraction that I need to pay attention to. Perhaps being a people person also helps -- I enjoy talking to and communicating with people, so I usually do not feel much of a burden when dealing with a departmental matter or a journal issue. I just feel lucky to be able to do all the things I love to do, and even get paid for some of them!*

Prof. Meng has been known as very unselfish with his time and effort when it comes to helping graduate students. One of his graduate students from the University of Chicago, Radu Craiu (now an assistant professor at the University of Toronto) recalls fondly his graduate student days. He would often find

Xiao-Li working around midnight in his office. Radu recalls: "Xiao-Li has truly brought the meaning of 'my office door is always open for my graduate students' to a new level. He once had a meeting with me that started at 11pm and ended at 1am. He has never given me the boot no matter how busy he was or how late I was in his office!" And many graduate students from the University of Chicago would agree.

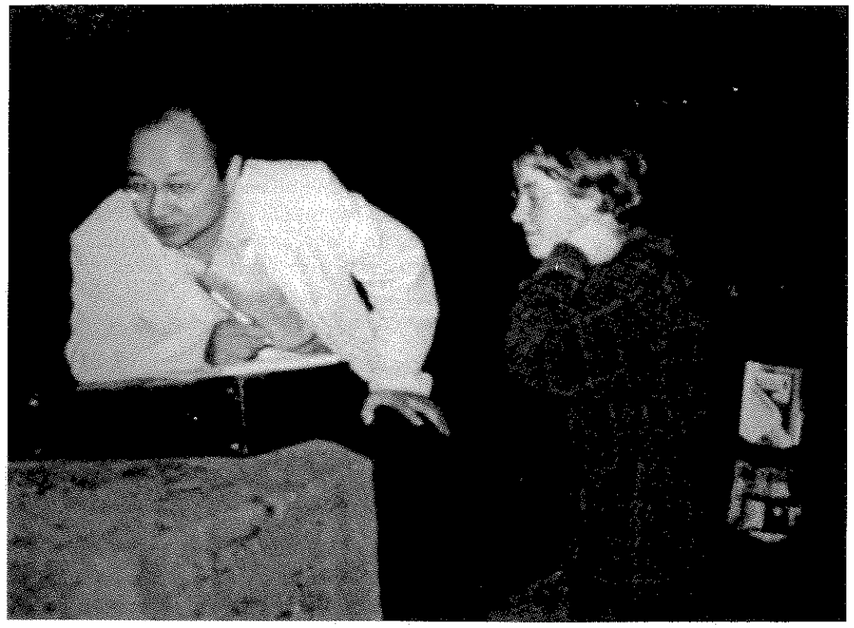
And Xiao-Li has always had time for other kind of problems as well – he was always there to motivate and help a student through a rough patch when one would come. We all had moments when we would get stuck on a problem and unavoidably get depressed. Xiao-Li had an uncanny ability to sense the "down times" and he would always come up with something to make everyone feel better. Again, Radu remembers: "He had one of the best encouragements for everyone: 'Just think about it logically: the harder the problem, the better we will feel when we solve it!' And this kind of care did not stop after graduation – I think Xiao-Li finds great pride in the accomplishments of his students and I have always felt that in his encouragement and help after graduation."

When Xiao-Li was invited to give a talk about George Tiao in honor of his 70th birthday at the ICSA Applied Statistics Symposium in San Diego, he kept coming back to the endless generosity and mentorship that Prof. Tiao has given not only to his students but also younger colleagues. There is a saying in Chinese that describes someone generous as "willing to give you the shirt off his back". I think each one of us who worked with Xiao-Li could say the exact same thing about him as well.

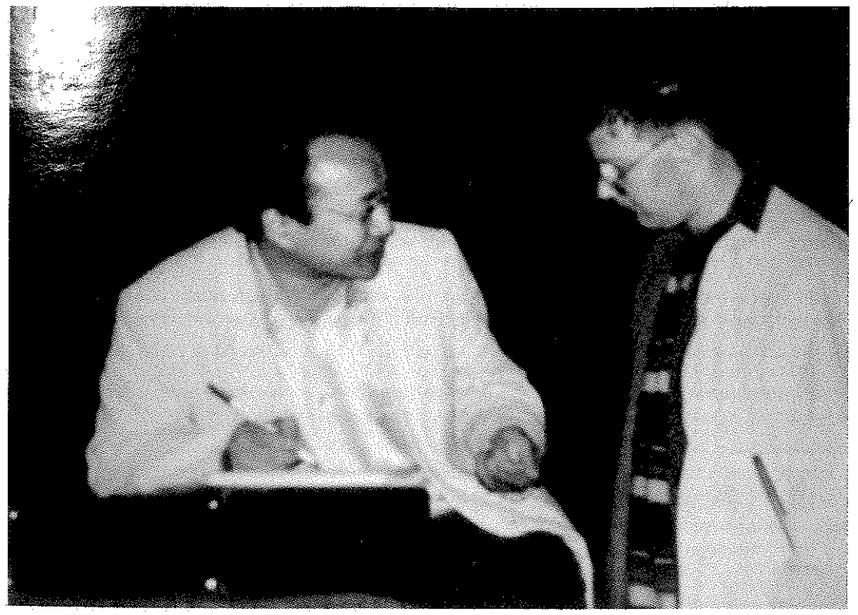
Love thy work and thou shall have fun -- What falls?

Prof. Meng has won an award for excellence in graduate teaching at the University of Chicago, and has not only taught but also inspired a number of students to pursue statistics. His passion for statistics is contagious, and it is hard not to get completely engrossed in the subject when working with him. The lessons we got from Xiao-Li on several occasions were so memorable and we still tell them to friends today.

In fact, Radu Craiu has reminded me of one of such occasions, when both of us were attending the Workshop on Monte Carlo Methods organized by the Fields Institute and the University of Toronto. We had both just started our graduate studies, and were very happy when, after days of lectures on perfect sampling, Xiao-Li proposed to take us to see Niagara Falls... Alas, there was an interesting random walk mentioned at one of the lectures that afternoon, and while driving us to the Falls, Xiao-Li started thinking out loud about the limiting distribution of that random walk. As we approached Niagara Falls, the proof was getting clearer and the discussion more heated, as Xiao-Li was writing on any available piece of paper we could find around. So here we were, for the first time at the magnificent Niagara Falls, trying to figure out the stationary distribution of a random walk on a finite state space with semi-absorbent edges... And despite the distraction offered by the Falls, we made it! (And we even have some photos to prove it!)



Random walk at Niagara Falls, Canadian Side, (with Vanja); October 26, 1998



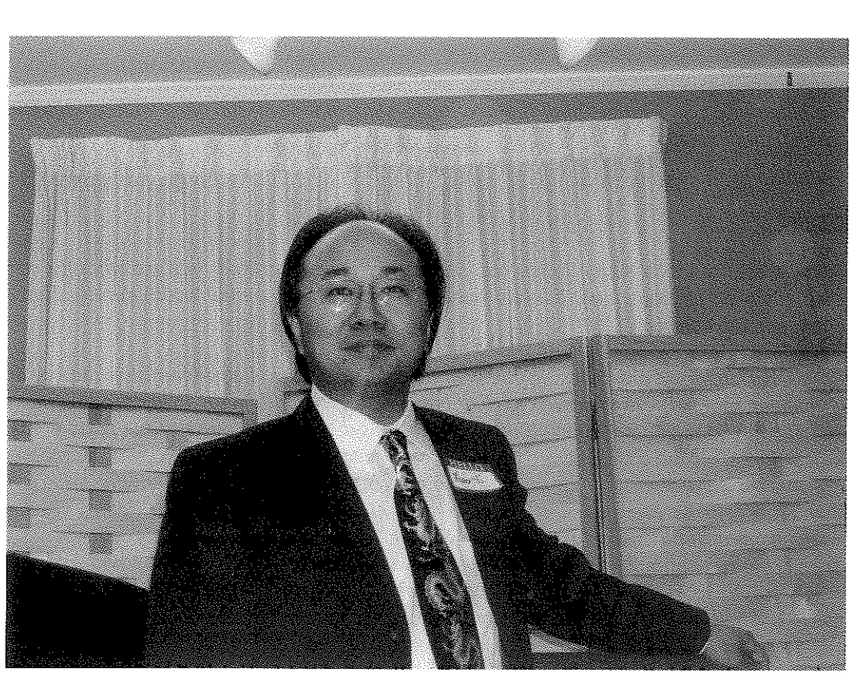
… and with Radu – "This must be right, right?"

Xiao-Li is a true perfectionist in his work, and he likes not only the correct proofs – he insists on elegant proofs. He has spent, well, years sometimes on certain concepts, and he tries to instill that in all his students. He always likes to tell a story about one of the theorems in his thesis (the rate of convergence of the ECM algorithm). It took him 5 days, without much sleep, to prove the theorem. And not because he couldn't do it in less time, but because he couldn't come up with a nice enough intuition behind the proof, that kept him up for 5 days. It turned out actually that the first proof was wrong, and getting the right intuition actually revealed the error! Xiao-Li recalls how amazed he was that his advisor, Don Rubin, after just having glanced at the proof simply said "Can't be!" which turned out to be right. He has insisted, since then, that the right intuition is as important as the right proof.

Social Scene

VMD: You have always been a great supporter of fun and socializing. Social life seems to play a large part in your life, and you always try to involve graduate students.

XLM: *Well, besides that obviously everyone likes to have fun, I am a big believer that a fun social environment helps to increase people's efficiency, be it for studying or for research. I'm therefore doing as much as I can to encourage and organize social activities in my department. In the past one and half years, we have had several Applied Probability Evenings (i.e., poker), an Applied Statistics Evening (i.e., Bowling), a movie night (with free entrance for anyone who has ever used or will use any data), and two holiday parties with talent shows with music and comedy performances… Everybody enjoys work more that way, and it is very rewarding.*



Hosting a Holiday Party at Harvard Statistics Department, December 15, 2004

Favorite pastimes

VMD: One of the first impressions you leave on people is that you love your work, so this may be a tough question for you. What do you enjoy the most about it?

XLM: *I love teaching, giving talks and brainstorming with students and collaborators the most. When I travel to work with friends, I actually get more done than when I stay in my office. Of course, I also enjoy immensely coming up with fun titles!*

VMD: How about your non-academic interests? You are well known for you love for food, wine, karaoke, and fishing!

XLM*: I should tell you my favorite fishing story. I went to visit Andrew Gelman, then at Berkeley, in the early nineties. Andrew decided to take me fishing, as he knew that I really like to fish and back in Boston we used to catch a lot of fish together. So Andrew had a high expectation. However, fishing is one of those highly uncertain activities, especially when you try a new location. So as it happened, two of us only caught one trout—I gather you can guess who was the master. (Laughter.) On our way back, Andrew said he wanted to stop by a local fish market. I was very curious, so I asked "Why?" "Well, since we always catch so much fish, I expected we would do the same today so I invited quite a few friends tonight to have a fish dinner party. But now we only have one fish ..." So to save the day (and our reputation!) we visited the local fish market, and Andrew made a lot of fish cakes after we got back to his apartment. Guess what? Those fish cakes fed Andrew for an entire week because shortly before the dinner time, a serious thunderstorm developed, so only Mary Sara Mcpeek (who was a Ph.D. student at Berkeley then) and her friend showed up! A great story, and lesson, about why prediction is so hard, especially if it is about future! (Laughter.)*

And I do enjoy wine, greatly. I find it goes really well with statistics—in statistics, I pursue simplicity; in wine, I seek complexity ... And nothing is more intoxicating than brainstorming with an inquisitive mind over a glass of silky velvet ...

Bridging fields

VMD: There seems to be so many things you are interested in. Currently you are working on so many projects, including perfect sampling, fractals, wavelets, biostatistics, mental health survey, digital camera demosaicing, and astrophysics ...

XLM*: I love being involved and learning about many different things. I am more fascinated by things that I know less about, and to me the greatest perk of being a statistician is what Tukey put succinctly: we get to play in everyone's back yard—actually these days we get to play in some of the front yards as well! And at places like Chicago and Harvard, one is surrounded by extremely intelligent people working on all sorts of fascinating topics. So I certainly would not let my curiosity remain only as such, even if that means that I need to be even more efficient in bed! (Laughter.) Even rediscovering someone else's methods, but from a statistician's perspective, can be extremely rewarding. For example, I was very proud of the bridge sampling and path sampling developed jointly with Wing Wong and Andrew Gelman. I was even more so when Andrew and I discovered that both were actually among the most powerful Monte Carlo methods that physicists have been using for years, because that means that we were as creative as some great physicists! (Laughter.)*

But Prof. Meng is also interested in trying new things outside of academia. He has always, for example, been interested in trying exotic foods, tasting funky new wine, or even tackling the slopes of Italian Alps

in Bormio without ever having skied before. Prof. Jeff Rosenthal (University of Toronto) has reminded us of a story about Xiao-Li's first skiing experience while at the MCMSki conference in January of 2005, when he decided to strap on a pair of skis and get to the top of a slope to ski down. We won't reveal what happened afterwards, but only that there were no missing parts of Xiao-Li that we needed to impute at the end of the day. But those kinds of curiosity have always followed Xiao-Li around.

Concluding remarks

VMD: So what are you most favorite aspects of being a statistician?

XLM: *As I said, being able to work on seemingly unrelated topics, interacting with great people from many fields, and learning something new and exciting almost every day!*

VMD: What is your least favorite aspect?

XLM: *The fact that statisticians prove the same theorems as economists, but have no chance for Nobel prizes; and that we sometimes have the same reputation as the lawyers, but are far less compensated for that! (Laughter)*

VMD: So what can you say to the future generation of junior statisticians?

XLM: *Really, just do it -- it's fun!! Also, drink more and sleep less ...*

Brainstorming with Vanja and Dan Nicolae (University of Chicago), at 2004 ENAR

...and more brainstorming with Radu and Dan ...

Special Feature Article

An Overview of Bridging Evaluations in Taiwan

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I. Introduction

Recently, geotherapeutics has attracted much attention from sponsors as well as regulatory authorities. However, the questions lie on when and how to address the geographic variations of efficacy and safety for the product development. It will strongly depend upon the size of the market, development cost, and the factors influencing the clinical outcomes for evaluation of efficacy and safety. If the size of the market for some new geographic region is sufficiently large, then it is understandable that the sponsor may be willing to repeat the whole clinical development program after the test product has completed its development plan and maybe obtain the market approval in the original region. Ideally, one of course can directly conduct studies in the new region with similar sample size to the phase III trials conducted in the original region for confirmation of the efficacy observed in the original region. Nonetheless, extensive duplication of clinical evaluation in the new region not only demands valuable development resources but also delay availability of the test product to the needed patients in the new regions. To address this issue, the International Conference on Harmonisation (ICH) has published a guideline entitled "*Ethnic Factors in the Acceptability of Foreign Clinical Data*" known as ICH E5 (1998).

A general framework is provided by the ICH E5 document for evaluation of the impact of ethnic factors on the efficacy, safety, dosage, and dose regimen. The ethnic factors are classified into the following two categories by the ICH E5 guideline. Intrinsic ethnic factors are factors that define and identify the population in the new region and maybe influence the ability to extrapolate clinical data between regions. They are more genetic and physiologic in nature, e.g., genetic polymorphism, age, gender, etc. On the other hand, extrinsic ethnic factors are factors associated with the environment and culture. Extrinsic ethnic factors are more social and cultural in nature, e.g., medical practice, diet, and practices in clinical trials and conduct. In addition, the ICH E5 guideline provides regulatory strategies of minimizing duplication of clinical data and

requirement of bridging evidence for extrapolation of foreign clinical data to a new region.

The ICH E5 guideline suggests that a bridging study be conducted in the new region to generate additional information to bridge the foreign clinical data when the foreign clinical data contained in the Complete Clinical Data Package (CCDP) can not provide sufficient bridging evidence. By the ICH E5 guideline, a bridging study is therefore defined as a supplementary study conducted in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen to allow extrapolation of the foreign clinical data to the population of the new region. In addition, the ICH E5 guideline also points out that evaluation of the ability of extrapolation of the foreign clinical data relies upon the similarity of dose response, efficacy, and safety between the new and original regions either with or without dose adjustment.

Taiwan government has identified biotechnology as one of the key technologies for Taiwan in the 21st century and biopharmaceutical industry as the most vital and important industry to succeed the semiconductor industry in Taiwan. Due to the intrinsic and extrinsic factors, the current Taiwan's registration trials can not adequately address the issue of extrapolation of the results from the original regions to the Taiwan's population. Therefore Taiwan has formally announced the implementation of the bridging study requirement. In Taiwan, the department of Health has successfully developed a sponsor self-evaluation check-list, a decision-making tree, and a consultation procedure. Requirement of bridging study evaluation (BSE) was formally announced on January 1, 2004. In other words, all products should go through bridging study evaluation from the year of 2004 afterwards.

II. Bridging Study Evaluation in Taiwan

By December 31, 2004, a total of 132 applications for BSE have been received and evaluated by the Department of Health of the Executive Yuan. Figure 1 illustrates the categorization of all BSE cases. Among these 132 applications, 121 have been completed and closed in which 82 cases were waived, 38 cases were not waived, and 1 was not related to BSE. Also, among the 121 completed cases, 51 did not provide Asian clinical and pharmacokinetic information. For those 51 cases, while Bridging Study was not waived in 19 cases, it was waived in the other 32 despite lack of Asian clinical and pharmacokinetic data.

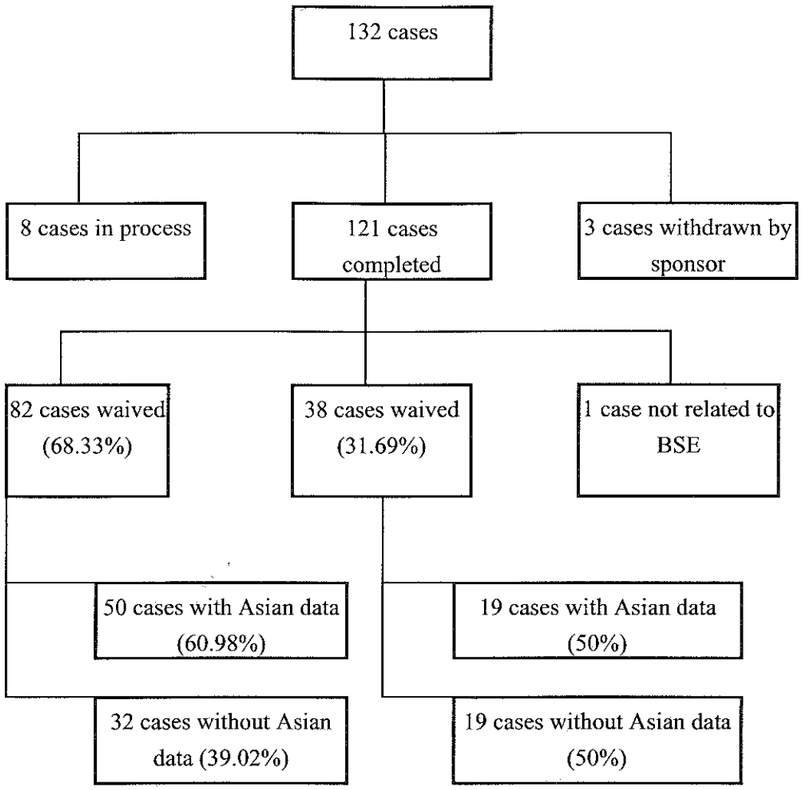

Figure 1. The categorization of all BSE cases by December 31, 2004. (Data are from CDE, Taiwan)

Figure 2 summarizes reasons for not waived bridging study. From those 38 cases, most common reasons for not waived bridging study are lack of pharmacokinetic information (71.1%), efficacy (55.3%), and safety concerns (47.4%).

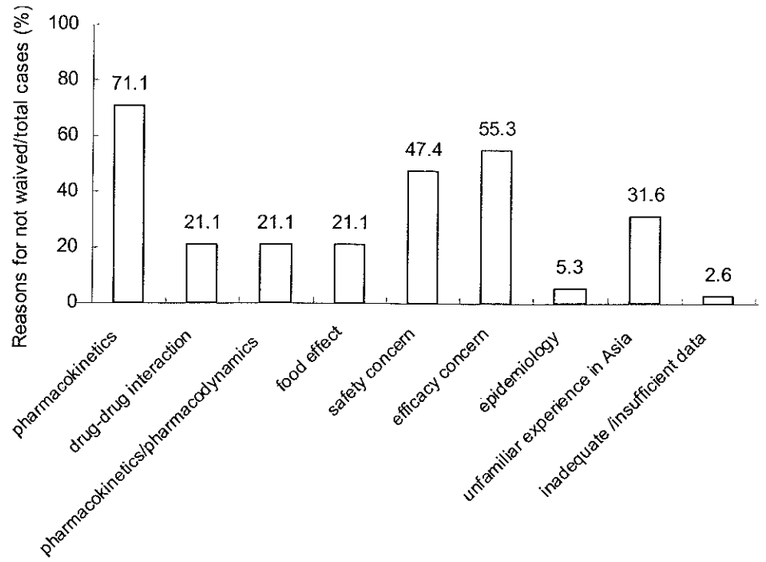

Figure 2. Reasons for not waived bridging study (Total case number: 38) (Data are from CDE, Taiwan)

III. Statistical Methodologies for Evaluation of Bridging Studies

Up to the present, the statistical work to draw a statistical inference with regard to bridging evidence is still in a preliminary stage.

(1) Bayesian approach to evaluation of bridging studies (Liu, Hsiao, and Hsueh, 2002)
A bridging study is conducted in the new region usually only after the test product is approved for commercial marketing because of its proven efficacy and safety. Sufficient information on efficacy, safety, dosage and dose regimen has been already generated in the original region and is available in the CCDP. Therefore, we can borrow the "strength" from the information on dose response, efficacy, and safety from the CCDP in the original region and incorporate them into the analysis of the additional data obtained from the bridging study. From the complete clinical data package, we can use the technique of meta-analysis to integrate the results from the original region to formulate the prior distribution for the test product and placebo. Based on the prior information, if the data collected from the bridging study in the new region also demonstrate a superior efficacy of the test pharmaceutical over placebo, then the efficacy observed in the population of the new region is claimed to be similar to that of the original region.

(2) Bayesian non-inferiority approach to evaluation of bridging studies (Liu, Hsueh, and Hsiao, 2004)

Liu, Hsiao, and Hsueh (2002) proposed an empirical Bayesian approach to synthesize the data generated by the bridging study and foreign clinical data generated in the original region for assessment of similarity based on superior efficacy of the test product over a placebo control. However, even if both regions have positive treatment effect, their effect sizes might in fact be different. That is, their approach could not truly assess the similarity between two regions. Therefore, we propose a Bayesian approach for assessment of similarity between the new and original region based on the concept of non-inferiority. More specifically, under the situation that the test product has been already approved in the original region due to its proven efficacy against the placebo control, if the data collected from the bridging study show that the efficacy of the test product from the new region is no worse than the efficacy of the test product from the original region by some clinically acceptable limit, then the efficacy observed in the bridging study in the new region can be claimed to be similar to that of the original region. This concept of similarity is referred to as similarity between the treatment effects from both new and original regions.

(3) Group sequential approach to evaluation of bridging studies (Hsiao, Xu, and Liu, 2003)
For these methods proposed above, the foreign clinical data provided in the CCDP from the original region and those from the bridging study in the new region were not generated in the same study and they are not internally valid. A group sequential method is therefore proposed to incorporate the information of the foreign clinical data into evaluation of the positive treatment effect observed in the new region within the same study. Within this framework, regions are treated as group sequence. When the study is completed in the original region, we then perform an interim analysis with the data from the original region. If the resulted test statistic does not cross the pre-specified boundary, then a bridging sub-study is not needed. On the other hand, if the results from the interim analysis based on the data of the original region show significant test product effect, then we proceed to enroll the patients in the new region. After the recruitment of the patients in the new region is completed, we then perform the final analysis with the additional data from the new region. If the results obtained for the final analysis are similar to those from the interim analysis, then the results of the new region can be declared similar to the original region. Here, the similarity is defined as the similar treatment effect to meet requirement of crossing the pre-specified boundary at the final analysis.

(4) A two-stage design for bridging studies (Hsiao, Xu, and Liu, 2005)
One of the drawbacks of the group sequential approach proposed by Hsiao, Xu, and Liu(2003) is that the determination of sample size is based on the fixed-sample-size approach. We therefore propose a two-stage design to incorporate the information of the foreign clinical data into evaluation of the positive treatment effect observed in the new region within the same study, and to compute the required sample size for each region subject to the constraints of the rates of the type I and type II errors. Within this framework, regions are treated as stages. In other words, patients from the original region are first enrolled into stage I of the

study and then the patients from the new region are enrolled subsequently in stage II of the study.

(5) Use of prior distributions for Bayesian evaluation of bridging studies
The results of the bridging studies using the approach developed by Liu, Hsiao, and Hsueh (2002) will be overwhelmingly dominated by the results of the original region due to an imbalance of sample sizes between the regions. In other words, it is very difficult, if not impossible, to reverse the results observed in the original region even the result of the bridging study is not consistent with those of the original region. However, this issue will occur for any methods for cross-study comparisons if the amount of information is seriously imbalanced between studies. Therefore, we propose a Bayesian approach with the use of a mixed prior for assessment of similarity between the new and original region based on the concept of positive treatment effect. In particular, the proposed prior is a weighted average of a non-informative prior and a normal prior.

IV. Summary

Recently, many Asian countries including Japan and Korea, have formally announced the implementation of the bridging study requirement. We may ask: is Taiwan on the right track? Nowadays, the increasing evidence that genetic determinants may mediate variability among persons in the response to a drug implies that patient responses to therapeutics may vary among racial and ethnic groups. In other words, after the intake of identical doses of a given agent, some ethnic groups may have clinically significant side effects, whereas others may have no therapeutic response. One example can be seen in Caraco (2004). Caraco points out that some of this diversity in rates of response can be ascribed to differences in the rate of drug metabolism, particularly by the cytochrome P-450 superfamily of enzymes. While ten isoforms of cytochrome P-450 are responsible for the oxidative metabolism of most drugs, the effect of genetic polymorphisms on catalytic activity is most prominent for three isoforms—CYP2C9, CYP2C19, and CYP2D6. Among these three, CYP2D6 has been most extensively studied and is involved in the metabolism of about 100 drugs including beta-blockers, antiarrhythmic, antidepressant, neuroleptic, and opioid agents. Several studies revealed that some patients are classified as having "poor metabolism" of certain drugs due to lack of CYP2D6 activity. On the other hand, patients having some enzyme activity are classified into three subgroups: those with "normal" activity (or extensive metabolism), those with reduced activity (intermediate metabolism), and those with markedly enhanced activity (ultrarapid metabolism). Most importantly, the distribution of CYP2D6 phenotypes varies with race. For instance, the frequency of the phenotype associated with poor metabolism is 5 to 10 percent in the Caucasian population but only 1 percent in the Chinese and Japanese populations.

Another example regarding the impact of ethnic factors on the responses to therapeutics is the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor

gefitinib (Iressa). Recently, Iressa was approved in Japan and the United States for the treatment of non-small cell lung cancer (NSCLC). The EGFR is a promising target anticancer therapy because it is more abundantly expressed in lung carcinoma tissue than in adjacent normal lung. However, clinical trials have revealed significant variability in the response to gefitinib with higher responses observed in Japanese patients than in a predominantly European-derived population (27.5% vs. 10.4%, in a multi-institutional phase II trial) (Fukuoka et al., 2003). Paez et al. (2004) also shows that somatic mutations of the EGFR were found in 15 of 58 unselected tumors from Japan and 1 of 61 from the United States. Treatment with Iressa causes tumor regression in some patients with NSCLC, more frequently in Japan. Finally, the striking differences in the frequency of EGFR mutation and response to Iressa between Japanese and U.S. patients raise general questions regarding variations in the molecular pathogenesis of cancer in different ethnic, cultural, and geographic groups.

Here we have two successful stories to tell. The drug with a fixed combination of 200mg dipyridamole and 25mg aspirin 1bid is used for prevention of recurrent stroke. After the standard process of BSE, we decided to request a bridging study due to an ethnic difference in medical practice (much lower dose for one of the components in Taiwan) and higher headache-associated dropout rate in the previous Philippine study. In the first four weeks, the local bridging study result showed that the headache dropout rate of patients with reduced dose 2 weeks and full dose 2 weeks was 6.7% which was not different from the dropout rate of placebo (8.7%), but was statistically different from the dropout rate of patients with full dose 4 weeks (16.3%). Consequently, Taiwan decided to change labeling's instruction for use.

Another drug is a new potent lipid-lowering agent. The PK study in the Japanese shows that Cmax of Japanese is 1.9 to 2.5 times of that for Caucasian while AUC is 2 to 2.5 times. Although the mean interracial difference is not substantial, Taiwan approved the drug with reduced maximal dosage due to the dose-dependent, drug-related rare SAE of rhabdomyolysis. The decision was further echoed by US FDA. After reviewing the results of a Phase IV PK study in Asian Americans, FDA urged the physician to reduce the starting dose and prescribe high dose with caution for Asians in labeling in March, 2005.

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Adaptive Design Methods in Clinical Trials

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1. INTRODUCTION

In clinical trials, it is not uncommon to adjust trial procedures and/or statistical methods during the conduct of clinical trials based on accrued data in order to identify clinical benefits of the test treatment under investigation (or increasing the probability of success of the trial). Trial procedures are referred to as the eligibility criteria, study dose, treatment duration, study endpoints, laboratory testing procedures, diagnostic procedures, criteria for evaluability, and assessment of clinical responses. Statistical methods include randomization, study design, study objectives/hypotheses, sample size, data monitoring and interim analysis, statistical analysis plan, and/or methods for data analysis. In this article, we will refer to the modifications made to the trial procedures and/or statistical procedures as the adaptive design methods. Thus, an *adaptive design* is defined as a design that allows modifications to trial procedures and/or statistical procedures of the trial after its initiation without undermining the validity and integrity of the trial (Chow, et al., 2005). In many cases, an adaptive design is also known as a *flexible* design.

The use of an adaptive design method for modifying the trial procedures and/or statistical methods of on-going clinical trials based on accrued data has been practiced for years in clinical research. An adaptive design method in clinical research is very attractive to clinical scientists due to the following reasons. First, it reflects medical practice in real world. Second, it is ethical with respect to both efficacy and safety (toxicity) of the test treatment under investigation. Third, it is not only flexible, but also efficient in the early phase of clinical development. However, it is a concern whether the p-value or confidence interval regarding the treatment effect obtained after the modification is reliable or correct. In addition, it is also a concern that the use of adaptive design methods in a clinical trial may lead to a totally different trial that is unable to address scientific/medical questions that the trial is intended to answer (EMEA, 2002).

In the next section, commonly employed adaptive design methods in clinical trials are described. Section 3 provides regulatory perspectives regarding the use of adaptive design methods in clinical trials. Challenges to the validity of adaptive design methods are given in Section 4. Brief concluding remarks are given in the last section.

2. ADAPTIVE DESIGN METHODS

In practice, adaptations or modifications made to trial procedures and/or statistical procedures during the conduct of a clinical trial are based on accrued data and/or as

recommended by an independent data monitoring committee. Commonly employed adaptive design methods in clinical trials include, but are not limited to: (i) a group sequential design, (ii) an N-adjusted design, (iii) a drop-the-loser design, (iv) an adaptive randomization design, (v) an adaptive dose-escalation design, (vi) a biomarker-adaptive design, (vii) an adaptive treatment-switching design, and (viii) a hypothesis-adaptive design. These adaptive design methods are briefly described below.

A group sequential design is an adaptive design that allows for prematurely terminating a trial due to efficacy or futility based on interim analysis results, while an N-adjusted design is referred to as an adaptive design that allows for sample size adjustment or re-estimation based on the observed data at interim. Drop-the-loser design is a multiple-stage adaptive design that allows dropping the inferior treatment groups. Adaptive randomization design refers to a design that allows modification of randomization schedules. Adaptive dose-escalation design is often used in early phase clinical development to identify the maximum tolerable dose, which is considered the optimal dose for later phase clinical trials. Biomarker-adaptive design is a design that allows for adaptations based on the response of biomarkers (or genomic markers). Adaptive treatment-switching design is a design that allows the investigator to switch a patient's treatment from an initial assignment to an alternative treatment if there is evidence of lack of efficacy or safety of the initial treatment. Hypothesis-adaptive design refers to a design that allows change in hypotheses based on interim analysis results.

It should be noted that the Bayesian and hybrid approaches in conjunction with clinical trial simulation are often considered when employing adaptive design methods in clinical trials (see, e.g., Chang and Chow, 2005). Other adaptive design methods in clinical trials can be found in a special issue entitled *Adaptive Design in Clinical Research* of the Journal of Biopharmaceutical Statistics (Pong and Luo, 2005).

3. REGULATORY PERSPECTIVES

In clinical trials, although the flexibility of modifying study parameters is very attractive to clinical scientists, several regulatory questions/concerns arise. First, what level of modifications to the trial procedures and/or statistical procedures would be acceptable to the regulatory authorities? Second, what are the regulatory requirements and standards for review and approval process of clinical data obtained from adaptive clinical trials with different levels of modifications to trial procedures and/or statistical procedures of on-going clinical trials? Third, has the clinical trial become a totally different clinical trial after the modifications to the trial procedures and/or statistical procedures for addressing the study objectives of the originally planned clinical trial? These concerns should be addressed by the regulatory authorities before the adaptive design methods can be widely accepted in clinical research and development.

In addition, from scientific/statistical point of view, there are some concerns regarding (i) whether the modifications to the trial procedures have resulted in a similar but different target patient population, (ii) whether the modifications of hypotheses have distorted the

study objectives of the trial, (iii) whether the flexibility in statistical procedures has led to biased assessment of clinical benefit of the treatment under investigation.

As a result, guidelines for adaptive design methods are necessarily developed to avoid every intentional or unintentional manipulation of the adaptive design results in clinical trials. The guidelines should describe in detail not only the standards for use of adaptive design methods in clinical trials, but also the level of modification in an adaptive design that is acceptable to the regulatory agencies. In addition, any changes in the process of regulatory review/approval should be clearly indicated in such guidelines. It should be noted that the adaptive design methods have been used in the review/approval process of regulatory submissions for years, though it may not be recognized until recently.

4. CHALLENGES TO CLINICAL SCIENTISTS

The use of adaptive design methods is very attractive to clinical scientists due to its flexibility. However, some concerns regarding the validity and integrity of the trials arise, which have become challenges to clinical scientists. In this section, some challenges regarding moving target patient population, adaptive hypotheses and adaptive group sequential design are discussed.

Moving Target Patient Population Any modifications made to the trial procedures and/or statistical procedures may introduce bias and/or variation to the data collected from the trial. Consequently, it may result in a similar but slightly different target patient population. We will refer to such a patient population as the *actual* patient population under study. As mentioned earlier, it is a concern whether (significant or major) changes made to the trial procedures and/or statistical procedures could lead to a totally different trial with a totally different target patient population. In addition, it is of interest to determine whether statistical inference obtained based on clinical data collected from the actual patient population could be applied to the originally planned target patient population. Chow, et al. (2005) suggested examining the performance of a proposed sensitivity index, in terms of changes in a shift and a scale parameter. This index measures the impact of the difference between the actual patient population and the original target patient population on statistical inference of the treatment effect. The challenge to clinical scientists is that both changes in the shift and the scale parameters could be random in real world clinical trials. In addition, sample sizes between protocol amendments and the number of protocol amendments are also random variables. In practice, *how to derive (unconditionally) statistical inference for the treatment effect* is a major challenge to biostatisticians.

Adaptive Hypotheses Modifications of hypotheses commonly occur during the conduct of a clinical trial due to the following reasons: (i) an investigational method has not yet been validated at the planning stage of the study, (ii) information from other studies is necessary for planning the next stage of the study, (iii) a need to include new doses, and (iv) recommendations from a pre-established data safety monitoring committee. In clinical trials with planned data monitoring for safety and interim analyses for efficacy, a recommendation for modifying or changing the hypotheses is commonly made after the

review of interim data. The purpose for such a recommendation is to ensure the success of the clinical trials for identifying the possible best clinical benefits to the patients who enter the clinical trials. We will refer to this process as adaptive hypotheses. In practice, adaptive hypotheses typically include (i) switching a superiority hypothesis to a non-inferiority hypothesis, (ii) switching a single hypothesis to multiple hypotheses or a composite hypothesis, (iii) switching primary study endpoints, (iv) dropping the losers, and (v) interchanging the null and alternative hypotheses. In practice, *how to provide an unbiased and fair assessment of the treatment effect under adaptive hypotheses* is a major challenge to biostatisticians.

Adaptive Group Sequential Design In practice, an adaptive group sequential design is often considered for (i) early stopping for clinical benefit or harm, (ii) early stopping for futility, (iii) sample size re-adjustment, and (iv) re-designing the study in mid-stream. The adaptive group sequential design is very popular due to the following two reasons. First, clinical endpoint is a moving target. The sponsors and/or investigators may change their mind regarding clinically meaningful effect size after the trial starts. Second, it is a common practice to request a small budget at the design and then one may seek for supplemental funding for increasing the sample size after seeing the interim data. To protect the overall type I error rate in an adaptive design with respect to changes in some design parameters, many authors have proposed procedures using observed treatment effects. This leads to the justification for the commonly used two-stage adaptive design, in which the data from both stages are independent and the first data are used for adaptation. *Protecting the overall type I error rate with respect to changes in some design parameters* has become a challenge to biostatisticians.

5. CONCLUDING REMARKS

From the clinical point of view, adaptive design methods reflect real clinical practice in clinical development. Adaptive design methods are very attractive due to their flexibility and are very useful especially in early clinical development.

From the statistical point of view, the use of adaptive methods in clinical trials makes current good statistics practice even more complicated. The validity of the use of adaptive design methods is not well established. The impact of statistical inference on treatment effect should be carefully evaluated under the framework of moving target patient population as the result of protocol amendments (i.e., modifications made to the study protocols during the conduct of the trials).

In practice, regulatory agencies may not realize that the adaptive design methods for review and approval of regulatory submissions have been employed for years without any scientific basis. Guidelines regarding the use of adaptive design methods must be developed so that appropriate statistical methods can be developed accordingly.

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Phase II/III Seamless Adaptive Design

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1 Seamless Phase II-III Designs

A seamless phase-II/III design is one of the most attractive adaptive designs. A seamless phase-II/III adaptive design is a combination of a phase II and phase III design that aims at achieving the primary objectives that are normally achieved through separate trials in phases II and III. In a seamless design, there is usually a so-called learning phase that serves the same purposes as a traditional phase-II trial, and a confirmation phase that serves the same objectives as a conditional phase III trial. Compared to traditional designs, a seamless design can reduce sample size and time-to-market for a positive drug candidate. In what follows, we will discuss different seamless designs and illustrate their utilities through examples. We will also discuss the issues and make recommendations on how to ensure the validity and integrity of a seamless trial.

There are many possible seamless designs. It is helpful to divide them into the following four different categories: (1) fixed number of regimens, which includes designs featuring early futility stopping, biomarker-informed early futility stopping, and early futility/efficacy stopping with N-re-estimation, (2) flexible number of regimens, which includes designs featuring a flexible number of regimens and hypothesis-adaptive and response-adaptive randomization, (3) population-adaptive, where the number of patient groups can be changed from the learning phase to the confirmation phase, and (4) combinations of (2) and (3). Note that in category 3, the patient groups are often correlated, e.g., whole patient population versus subpopulation with certain genomic markers. When all patient groups are mutually independent, then categories 3 and 4 are equivalent statistically.

Different designs in category 1 have been discussed by Chang (2005), and a Bayesian biomarker-adaptive design has been proposed by Chang (2006). The foci will be on seamless designs with a flexible number of regimens. We will compare four different seamless designs with normal endpoints, each having five treatment groups including a control group in the learning phase. Because of multiple-group trials, contrast tests are used for detecting treatment difference with the null hypothesis test of $H_o : \Sigma_{i=1}^5 c_i u_i > 0$, where c_i is the contrast for the i^{th} group that has an expected response of u_i. The test statistic is defined as $T = \Sigma_{i=1}^5 c_i \hat{u}_i$.Five seamless designs are considered: (1) five-arm group sequential, (2) hypothesis adaptive, where contrasts c_i change dynamically according to the response shape (u_i) to gain the most power and an inferior arm will be dropped if its observed response worse than the control, (3) drop-losers,

where inferior groups (losers) will be dropped, but 2 groups and the control will be kept in the confirmation phase, and (4) keep-winner, which keeps the best group and the control at the confirmation phase. Because the maximum power is achieved for a balanced design when the shape of the contrasts is consistent with the shape of the response (Stewart &Ruberg, 2000; Chang & Chow, 2006; Chang, 2006), in the hypothesis-adaptive approach, the contrasts in the confirmation phase are reshaped based on the observed responses in the learning phase. Three different response and contrast shapes are studied (Table 1). The powers of the adaptive designs are summarized in Table 2, where the generalized Fisher combination method (Chang 2005) with efficacy and futility stopping boundaries of $\alpha_1 = 0.01, \beta_1 = 1, \alpha_2 = 0.0033$ is used. It can be seen that the keep-winner design is very robust for different response and contrast shapes.

Table 1: Response and Contrast Shapes

Shape	u_1	u_2	u_3	u_4	u_5	c_1	c_2	c_3	c_4	c_5
Monotonic	1.0	2.0	3.5	4.0	4.5	-1.9	-0.9	0.1	1.1	1.6
Convex	1.0	1.0	4.0	1.0	3.0	-1.0	-1.0	2.0	-1.0	1.0
Step	1.0	3.4	3.4	3.4	3.4	-1.92	0.48	0.48	0.48	0.48

Table 2: Power (%) of Contrast Test

		Contrast		
Response	Design	Monotonic	Wave	Step
Monotonic	Sequential	96.5	27.1	71.0
	Adaptive	83.4	50.0	70.0
	Drop-losers	71.2	71.2	71.2
	Keep-winner	84.8	84.8	84.8
Wave	Sequential	26.5	95.8	23.3
	Adaptive	49.5	82.1	48.0
	Drop-losers	47.8	47.8	47.8
	Keep-winner	60.7	60.7	60.7
Step	Sequential	42.6	14.6	72.4
	Adaptive	41.0	26.4	54.6
	Drop-losers	72.7	72.7	72.7
	Keep-winner	83.3	83.3	83.3

Note: $\sigma = 10$, one-sided $\alpha = 0.025$, interim n = 64/group.
Expected total n = 640 under the alternative hypothesis for all the designs.

2 Why a Seamless Design Is Efficient

How can seamless designs increase efficiency? Savings are created when a drug is not working through early stopping for futility; savings are also created when a drug has a dramatic effect by early stopping for efficacy. Time is

saved because there is no gap between the learning and confirmation phases. Savings are created by reusing data in the learning phase at final analysis. The most distinguished feature of the seamless phase II/III design is that there are differences in controlling type-I error rate (alpha) and power between a seamless design and the traditional design with separate phase II and phase III trials: In traditional designs, the actual $\alpha = \alpha_{II}\alpha_{III}$, where α_{II} and α_{III} are the type-I error controlled at phase II and phase III. If two phase III trials are required, then $\alpha = \alpha_{II}\alpha_{III}\alpha_{III}$. In a seamless phase II/III design, actual $\alpha = \alpha_{III}$. If two phase III trials are required, then $\alpha = \alpha_{III}\alpha_{III}$. Therefore, the α for a seamless design is actually $1/\alpha_{II}$ times larger than the traditional design. Similarly, we can steal power (permissible) by using a seamless design. Here power refers to the probability of detecting a "true" but not "hypothetical" treatment difference. In a classic design, the actual power = Power_{II} Power_{III}, while in a seamless phase II/III design, actual power = Power_{III}. Therefore, the power for a seamless design is $1/power_{II}$ times larger than the traditional design.

3 Validity and Integrity of Seamless Adaptive Trials

It is crucial to ensure the validity and integrity of a seamless trial. Preservation of the type-I error (alpha) is essential, but alpha $\neq$ Validity + Integrity must also be preserved. The validity of a trial includes internal and external validities. Internal validity refers to the degree to which we are successful in eliminating confounding variables and establishing a cause-effect relationship (treatment effect) within the study itself. A study that readily allows its findings to generalize to the population at large has high external validity. There are many different ways that the internal validity of a study can be threatened or jeopardized. Threats to internal validity include instrumentation (CRF, coding shift, evaluation criteria), selection bias (randomization failed at some level, e.g., a less-sick patient may prefer to wait for enrollment in the confirmation stage instead of the learning stage, but a sicker patient may not be able to wait, which will cause bias when response-adaptive randomization), and experimental mortality (informed dropouts). The threats to external validity are protocol amendments, including exclusion/inclusion criteria changes which lead to a target population shift (Chow, Chang & Peng, 2005), and multiple-endpoints that do not support a common conclusion.

Statistical validity can be addressed through three aspects: alpha control, adjusted p-value, and adjusted mean and confidence interval.

(1) Alpha-control

Due to multiple looks or analyses in a seamless adaptive design, the type-I will be inflated. There are many valid statistical methods to control alpha-inflation for adaptive designs, such as (1) Different combination of independent p-values from subsamples collected between two consecutive adaptations

(Bauer & Kohne, 1994 and Bauer & Rohmel, 1995; Lehmacher and Wassmer, 1999; Wassmer, Eisebitt and Coburger, 2001; Chang 2006), (2) Weighting the samples differently before and after each adaptation (Cui, Hung & Wang 1999), (3) Conditional error function approach (Proschan & Hunsberger, 1995 and Liu & Chi, 2001), (4) Conditional power approach (Posch & Bauer, 2000), and (5) Simulation method (Chang, 2005; Chang, Chow and Pong, 2005). Using simulation, we can easily find the dropping boundaries that will control the alpha. Also, simulation gives a great freedom in choosing a test statistic with minimal assumptions.

(2) The adjusted p-value is a little bit more complicated. It is dependent on how the "more extreme" is defined, and the definition is associated with the analysis stage at which the test statistic calculated. Stopping boundaries alone usually do not sufficiently define the method of calculating adjusted p-values. Analytical forms of adjusted p-values are dependent on the distribution of the test statistic under the null hypothesis, the analytical form of which is often not available for adaptive designs. On the other hand, simulation can generate the distribution of the test statistic easily for virtually any adaptive design; this is also the case with the adjusted p-values. So far, there are limited discussions of adjusted p-values for adaptive designs.

(3) Adjusted mean and confidence interval

There are some research results on unbiased estimators, such as the drop-the-losers design (Sampson & Sill, 2005). However, whether the adjusted or unadjusted mean should be used is philosophically debatable. Let's discuss the conditional δ_c and unconditional means δ for both classic and adaptive designs. For normal response, the conditional mean is the mean under the condition that the null hypothesis of no treatment effect is rejected. It can be derived that the relative bias of the conditional mean for a classic design with two independent groups is given as

$$\frac{\delta - \delta_c}{\delta} = \frac{1}{1-\beta}\frac{\sigma}{\delta\sqrt{\pi n}}\exp\left(-\frac{1}{2}z_{1-\beta}^2\right).$$

where β is the type error, σ is the standard deviation, and n is the sample size per group. It is true that what we submitted to FDA reviewers is a conditional mean that is biased. For $\beta = 0.2$, there is about a 12% bias for a classic design. Whether a conditional or unconditional mean was submitted to the FDA, the FDA will approve (a subset of) the conditional mean anyway. Therefore, what patients see is most biased. Now the question is what to report: conditional or unconditional mean? Should the conditional mean be adjusted since it is reported to patients and it is biased for both classic and adaptive designs?

Ensuring the integrity is also critical in a seamless design. Integrity means a solid protocol design, excellent execution, unbiased analyses of trial data, and correct interpretation of the results. Integrity means being ethical and avoiding the out-weighting of the risk-benefit ratio of individual patients, trial patients as a whole, and future patients. Integrity also means that regulatory agencies use appropriate approval criteria that balance the risk and benefit.

The use of a fixed type-I error rate criterion might, in fact, prevent a low-risk and low-benefit drug from being delivered to patients.

It is recommended that a seamless design be theoretically valid, which may be accomplished through simulations, practically feasible, which means better planning is necessary; anticipation of, and robustness against, protocol deviation, which means careful monitoring, are also necessary.

4 Summary

Seamless phase II/III adaptive design methods represent a new territory in drug development. Using adaptive designs, we can increase the chance of the success of a trial with a reduced cost. Bayesian approaches provide a new tool for optimizing trial design and development planning by utilizing/integrating all the relevant knowledge and information available. Clinical trial simulations offer a powerful tool to design and monitor trials. The combination of adaptive design, the Bayesian approach and trial simulation forms an ultimate statistical instrument for most successful drug development programs.

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Member News for Dr. Hulin Wu

Biodefense Center Grant (Contract) Awarded to an ICSA Member

Dr. Hulin Wu, Professor of Biostatistics at the Department of Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry (New York, USA) and permanent member of ICSA, recently received a grant of about $10 million in total over 5 years from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) to establish a Center for Biodefense Immune Modeling (CBIM). The award acknowledges the importance of statistical leadership in the development of quantitative models of immune response to native and hypothetical biopathogens and simulation tools to test *in silico* the efficacy of potential countermeasures to bioengineered biopathogens.

The University of Rochester (UR) is one of four institutes selected to establish Centers for Modeling Immunity for Biodefense by NIH. The other three Center contracts were awarded to Duke University Medical Center, Mount Sinai School of Medicine and the University of Pittsburgh. The University of Rochester's CBIM, led by Dr. Hulin Wu, Principal Investigator (PI) of this project and Director of the CBIM, consists of 3 cores including a Mathematical Modeling Core, Statistics/Data Management Core, and Bioinformatics/Computing Core, as well as 5 immunology labs. Dr. Martin Zand (MD), Associate Professor of Medicine, University of Rochester, is the Co-Director who will assist Dr. Wu in directing and coordinating immunological experiment research. An education program will also be established within the Center. The objectives of the CBIM are to 1) develop mathematical/computational models to simulate immune response to influenza A virus, both native and hypothetical bioengineered strains, 2) design and conduct laboratory experiments to identify, measure and validate the immune response models, 3) develop statistical methods and user-friendly computer software for immunology data analysis, model identification and prediction, 4) develop a Web server-based software application to provide the bioinformatics component of this project, 5) investigate the feasibility of extending influenza A virus models to vaccinia virus for immune response simulations, and 6) provide an education program to educate multidisciplinary researchers on the power of applying mathematical/statistical principles to immunology and biodefense.

It is rare for a statistician to serve as a PI for a large multidisciplinary biomedical research project. However, this award provides proof that a statistician can play an important role and take a leadership position in biomedical research if we closely collaborate with biomedical scientists and intelligently apply our expertise in mathematical modeling and statistics to practical scientific research issues. Dr. Hulin Wu received his Ph.D. training in statistics from Florida State University in 1994 and visited the University of Memphis from 1994-1996. He

was a Senior Statistical Scientist and later a Principle Research Scientist at Frontier Science and Technology Research Foundation (FSTRF) from 1996-2003, a non-profit institute, founded by Prof. Marvin Zelen, Harvard University, where he worked for the Statistical and Data Analysis Center (SDAC) of the AIDS Clinical Trials Group (ACTG), a key project in the Center for Biostatistics in AIDS Research (CBAR), Harvard School of Public Health. In 2003, he accepted the position of Professor at the Department of Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry. He also serves as Chief of the UR's Division of Biomedical Modeling and Informatics and holds faculty appointments in the Department of Medicine and Department of Community and Preventive Medicine at the UR. Besides this Biodefense Center contract, Dr. Wu is also directing two other NIH-sponsored projects (RO1 grants) with a total budget of $2 million in direct costs. The objectives of these RO1 projects are to develop mathematical modeling tools and statistical methods for HIV/AIDS research.

The Department of Biostatistics and Computational Biology, University of Rochester has tripled its faculty size in the past 3 years and expanded its research program in various directions to include computational biology, cancer modeling, and infectious diseases and immunology modeling. This center award is another great addition to the Department, allowing for further expansion by necessitating the recruitment of new faculty members and research associates (including database and software developers). Job openings can be found on the Department's website (http://www.urmc.rochester.edu/smd/biostat).

OBITUARY of XIRU CHEN *(陈希孺院士)*: 1934-2005

XIRU CHEN, Professor of statistics at the graduate school of Chinese Academy of Sciences (CAS), passed away on August 8, 2005 in Beijing, China, at the age of 71. He is survived by his beloved wife, Xichun Zhu, his son Ming Chen, his daughter Lan Chen, and two grandchildren.

Xiru Chen was born on February 11, 1934, in Hunan, China. He graduated from Department of Mathematics, Wuhan University in 1956. He was employed by the Institute of Mathematics, CAS, from 1956 to 1960, then he held faculty positions at University of Science and Technology of China (1960-1986), graduate school of CAS (1986-2005) and was visiting University of Pittsburgh, Columbia University, University of California, Berkeley, University of Wisconsin - Madison, Academia Sinica, Taiwan, and several other universities in the United States, Canada, China, Hong Kong and Taiwan. Due to his significant contributions to mathematical statistics, he was honored by being elected as CAS academic member in 1997, and was an elected fellow of Institute of Mathematical Statistics and an elected member of International Statistical Institute.

Chen's scientific achievement was highlighted by his works in large sample theory in parametric and nonparametric statistics. He had made significant contributions to the following areas: (i) asymptotic theory for linear models, (ii) Berry-Essen bounds and Edgeworth expansion, (iii) limit theorems for U-statistics, (iv) nonparametric statistics and (v) density estimation and nonparametric regression and smoothing. His research results are theoretically profound and statistically important. He published more than 130 papers in leading statistical and mathematical journals and 10 monographs and textbooks.

Chen was among the few in China who initiated theoretical researches and education in statistics after the Cultural Revolution. In 1980's, he organized a series of workshops introducing advanced statistical methodologies as well as large sample research topics which had inspired many young researchers into the frontiers of statistics. A great many people owe a lot to him for his generous help in their career development. He supervised all the three students of statistics among the first eighteen Ph.D. degree recipients from different areas since after the establishment of PR China. Today, his influence can be felt from almost all statistics-related places across the whole country. His formal and informal students are playing the major roles in Chinese community of statistics. He founded and was elected as the first co-president of the Chinese Society of Probability and Statistics in 1980 and was the president of Chinese Association for Applied Statistics (CAAS). He was actively involved in the editorial board of 9

statistical or mathematical journals in China and overseas.

Xiru Chen devoted his life to scientific activities and statistical education. His influence in the development of statistical science in China is profound and everlasting. He is warmly remembered by his students, colleagues, and friends as being a distinguished academician, dedicated advisor, and a great mentor.

Regional Activities

Hong-Kong

Hailiang Yang, Ph.D.

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) presented papers. For more details, please visit the workshop website at: http://www.hku.hk/statistics/workshop.

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

This conference was held from June 20-24, 2005 at Hong Kong Baptist University. The conference was 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, distinguished speakers, and plenary speakers including 15 well known statisticians. The scientific committee chairmen were Jianqing Fan (Princeton University) and Fred J. Hickernell (Hong Kong Baptist University) and the local organising committee chairman was 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 was organized by The International Association for Statistical Computing (IASC), Asian Regional section and co-organized by the Hong Kong Statistical Society and the Department of Statistics and Actuarial Science, The University of Hong Kong. The Keynote speakers were Professors Peter Hall (Australia National University) and Tze-Leung Lai (Stanford University). The conference chair was W.K. Fung (The University of Hong Kong); co-chairs were Y. Tanaka (Nanzan University) and J. C. Lee (Korea University). The organizing committee chair was K.C. Yuen (The University of Hong Kong) and the Scientific Programme Committee chair was 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 held a conference on 17 December 2005. The organizing committee chair was W.K. Fung (The University of Hong Kong) and the scientific committee chair was M.S.S. Lee (The University of Hong Kong). The keynote speaker was 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 was 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 gave talks during the conference. For more details, please visit http://www.hku.hk/math/imr or http://www.hku.hk/statistics/Conference/CPAFI-2st.htm.

Department of Statistics and Actuarial Science, HKU

Professor W.K. Li has been the head of Department of Statistics and Actuarial Science of the University of Hong Kong starting from January 1, 2006. The appointment is for three years.

Census and Statistics Department

Mr. Fung Hing-wang has been appointed as Commissioner and Mr. Dominic Leung Kam-to has been appointed as Deputy Commissioner of the Census and Statistics Department since August 2005. The former Commissioner, Mr. Frederick Ho Wing-huen is on pre-retirement leave.

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

Taiwan

C. Andy Tsao, Ph.D.

Recent Statistical Conferences and Workshops in Taiwan

2005 Annual Conference of Chinese Statistical Society

December 10, 2005. Tamkang University, Tamsuei, URL: http://www.stat.tku.edu.tw/stat.

Statistics and Probability Conference in Memory of Ching-Zong Wei

December 12-14, 2005. Institute of Statistical Science, Academia Sinica, Taipei, URL:http://www3.stat.sinica.edu.tw/2005wei/index.htm.

TMS & AMS Joint International Conference

December 14-18, 2005. Tunghai University, Taichung, URL:http://www.math.thu.edu.tw/2005ims/en/index.htm.

Statistics and Machine Learning Conference 2006 in Taiwan

July 24-28, 2006. Academia Sinica, Taipei, URL: Statistics and Machine Learning Conference 2006 in Taiwan.

Machine Learning Summer School (MLSS Taipei 2006)

MLSS Taipei 2006 is the 2006 version of the "Machine Learning Summer School" series held previously in Canberra, Tubingen, Berder and Chicago. July 24 - August 4. Institute of Statistical Science and Institute of Information Science, Academia Sinica, Taipei, URL: http://www.iis.sinica.edu.tw/MLSS2006.

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

Some Upcoming Statistical Meetings

ICSA 2006 Applied Statistics Symposium, June 14-17, 2006

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 (Refer to ICSA website http://www.icsa.org).

The 2006 International Conference on Design of Experiments and Its Applications, July 9-13, 2006

The "2006 International Conference on Design of Experiments and Its Applications" will be held at Nankai University in Tianjin, China, July 9-13, 2006. The focus of this conference is on recent developments in the theory and application of Design of Experiments and related areas. The principal aim is to provide a forum for exchanging ideas. The detailed information is now available on the conference's web site at http://stat.math.nankai.edu.cn/doe.htm and http://202.113.29.3/~stat/doe.htm. Please contact Professor Minqian Liu, Department of Statistics, School of Mathematical Sciences, Nankai University, Tianjin 300071, CHINA <mqliu@nankai.edu.cn>.

IBC2006: XXIII International Biometrics Conference, July 16-21, 2006

The 2006 International Biometrics Conference, sponsored by the International Biometric Society, will be held in Montreal, Quebec, Canada. The 2006 XXIII International Biometrics Conference brings together statisticians and bioscientists interested in the development and application of statistical and mathematical methods for the biological sciences. (Refer to the website www.ibc2006.org).

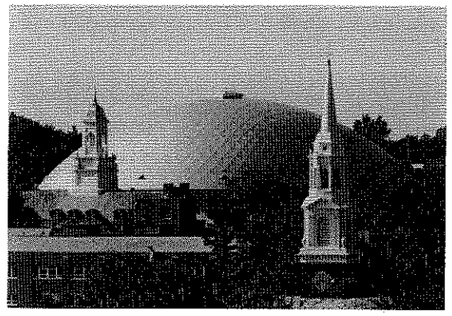
The 2006 Joint Statistical Meetings, August 6-10, 2006

JSM (the Joint Statistical Meetings) is the largest gathering of statisticians held in North America. It is held jointly with the American Statistical Association, the International Biometric Society (ENAR and WNAR), the Institute of Mathematical Statistics, and the Statistical Society of Canada. Attended by over 5500 people, activities of the meeting include oral presentations, panel sessions, poster presentations, continuing education courses, exhibit hall (with state-of-the-art statistical products and opportunities), placement service, society and section business meetings, committee meetings, social activities, and networking opportunities. Seattle is the host city for JSM 2006 and offers a wide range of possibilities for sharing time with friends and colleagues. For information, contact jsm@amstat.org or phone toll-free (800) 308-8943. (Refer to the website http://www.amstat.org).

ICSA 2006 Applied Statistics Symposium

June 14-June 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.

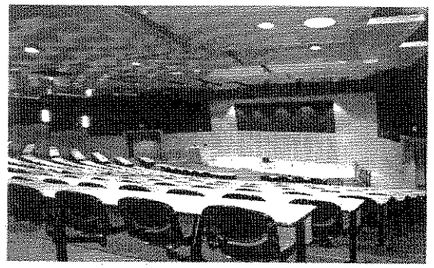


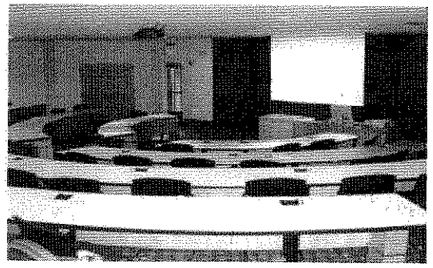
Organized by the International Chinese Statistical Association, this annual statistics symposium will feature three keynote talks by Professors James O. Berger of Duke University and SAMSI, Xiao-Li Meng of Harvard University, and Terrence P. Speed of the University of California at Berkeley and the Walter 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. The Banquet Speaker will be Dr. Henry Lee, Chief Emeritus of the Connecticut State Police. 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 two 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, Department of Statistics, University of Connecticut, email: mhchen@stat.uconn.edu.

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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.

ICSA 2006 Applied Statistics Symposium
Short Courses Announcement

The 15th annual ICSA Applied Statistics Symposium will be held at the University of Connecticut's main campus in Storrs, Connecticut, USA. In this symposium, eight short courses will be offered. Out of these eight short courses, three are half-day, and five are whole day courses. Descriptions of these courses are given below. All eight courses will be filled up quickly. Please register at the ICSA 2006 website, www.stat.uconn.edu/ICSA2006, for short courses as soon as possible.

Course 1: Statistical Models and Analysis for Financial Data (AM Session)

Professor Yazhen Wang (University of Connecticut) will teach this short course. In asset pricing and financial econometrics, complex stochastic models have been employed, and cutting-edge statistical methods are being used for inferences and computations. For these complex models, efficient computational methods are in great demand for simulations, derivative pricing and statistical inferences. This short course will concentrate on statistical computing and inferences of these models for discrete-time financial data. It will cover Monte Carlo simulation of nonlinear models such as GARCH models, stochastic volatility models and diffusion models and discuss statistical inferences of the models for financial data like daily stock return and currency exchange rate as well as high-frequency financial data. Applications of these nonlinear models in derivative pricing and risk management will be illustrated.

Course 2: Contributions to Discrete Distributions (PM Session)

Professor Daniel Zelterman (Yale University) will discuss the development of methods for deriving new discrete distributions. Specific examples will be motivated by studies of data from the fields of medicine, demography, and pre-clinical drug development. We begin with general principles for discrete distributions such as the binomial and hypergeometric models. From these we can generalize the principles to demonstrate how new distributions may be derived. The first half of the course describes relevant urn models. While urn models provide a simple teaching tool, these lack practical application. Instead, we will motivate the models using examples involving frequencies of birth defects in litters of laboratory animals and models for estimating frequencies of genetic markers in the population. The second half of the short-course describes models for sums of dependent Bernoulli random variables. Once we drop the assumption of independence, the level of mathematical difficulty rises quickly.

Nevertheless, there are several relatively simple and useful methods for deriving distributions for sums of dependent 0-1 Bernoulli random variables. We motivate these new distributions using studies of drug toxicity in a pre-clinical study of birth defects in laboratory animals.

Course 3: Design and Analysis of Dose Response Trials (PM Session)

Dr. Naitee Ting (Pfizer) will cover the design of dose response clinical trials, and Dr. James MacDougall (Bristol-Myers Squibb) will present how to analyze the data obtained from these trials.

In the process of drug discovery and drug development, understanding the dose response relationship is one of the most challenging tasks. It is also critical to identify the right range of doses in early stages of clinical development so that Phase III trials can be designed to confirm the efficacy and safety of these doses.

For study design, the thinking process should start way before a drug candidate enters Phase II. Scientists need to make best use of data obtained from pre-clinical experiments and early Phase I trials, to learn from other drugs of the same class, and to understand the PK and PD properties of the drug candidate. It is also important to consider the formulation, the potential market environment and other similar drugs that may compete with the candidate under study. All these are important considerations for designing the dose response studies.

After the dose response clinical data are collected, many statistical approaches are available to perform data analysis. The two main categories are modeling approaches and multiple comparison adjustments. Depending on stage of development and objectives of the study, appropriate method will be selected for data analysis. The usefulness of each approach under various situations will be discussed in this short course.

Course 4: Active Controlled Trials (Whole Day Session)

Dr. Yi Tsong (Food and Drug Administration) will cover this course in 4 sections:

Section 1: *Bioequivalence trials*
In-vivo bioequivalence trials with test and reference drugs

- Average bioequivalence assessment
- Sequential design considerations
- Average bio-in-equivalence challenge test
- Population bioequivalence and individual bioequivalence

Clinical bioequivalence trials with test, reference and placebo arms

- Comparison of means
- Comparison of response rates
- Sequential design considerations
- Sample size estimation
- Adaptive sample size estimation for variable drop-out rate

Section 2: *Two-arm superiority and non-inferiority active controlled clinical trials I*

Objectives –

- Superiority testing
- Putative for efficacy over placebo
- No worse than active control treatment
- Preserving a percentage of efficacy of active control treatment

Designs –

- Generalized historical control approach
- Cross-trial comparison approach
- Margin determination
- Sample size determination
- Multiple testing of superiority and non-inferiority

Section 3: *Two-arm superiority and non-inferiority active controlled clinical trials II*

Issues beyond simple two sample comparison –

- Switching analysis model
- Sequential and adaptive design
- Two pivotal trials and data dependence
- Homogeneity assessment

Efficacy measurements of binary outcome data –

- Odds ratio
- Responding rate difference
- Ratio of responding rates

Section 4: *Other active controlled clinical trials*

- Non-inferiority cohort or case-control trials
- Drug abuse potential trials
- QT/QTc prolongation trials

Course 5: Bayesian Methods for Survival and Longitudinal Data (Whole Day Session)

Professor Joseph Ibrahim (University of North Carolina) and Professor Ming-Hui Chen (University of Connecticut) will also cover the course in 4 sections. Survival methods are becoming increasingly popular in analyzing survival and longitudinal data in many fields of study such as medicine, biology, engineering, public health, epidemiology, and economics. This short course aims to provide a comprehensive treatment of semiparametric Bayesian methods for survival and longitudinal data. There will be four 2-hour sessions.

Session 1. Bayesian Semiparametric Survival Models

In this session, we will discuss Bayesian models based on prior processes for the baseline hazard and cumulative hazard, construction of the likelihood function, prior elicitation, and computational algorithms for sampling from the posterior distribution. We will discuss gamma processes, beta processes, and correlated gamma processes. Several examples and case studies will be presented to illustrate the various models.

Session 2. Bayesian Cure Rate Models

Survival models incorporating a cure fraction, often referred to as cure rate models, are becoming increasingly popular in analyzing data from cancer clinical trials. The cure rate model has been used for modeling time-to-event data for various types of cancers, including breast cancer, non-Hodgkins lymphoma, leukemia, prostate cancer, melanoma, and head and neck cancer, where for these diseases, a significant proportion of patients are "cured." In this session, we will give a comprehensive Bayesian treatment of the cure rate model and discuss its applications in cancer. We will also present a multivariate extension of the cure rate model, and discuss its computational implementation in detail. In addition, we will discuss informative prior elicitation for this model based on the power prior, and discuss its properties. Several case studies will be presented to illustrate these models.

Session 3. Joint Models for Longitudinal and Survival Data

In this session, we will discuss joint models for longitudinal and survival data. Joint models for survival and longitudinal data have recently become quite popular in cancer and AIDS clinical trials, where a longitudinal biologic marker such as CD4 count or immune response to a vaccine can be an important predictor of survival. Often in clinical trials where the primary endpoint is time to an event, patients are also monitored longitudinally with respect to one or more biologic endpoints throughout the follow-up period. This may be done by taking immunologic or virologic measures in the case of infectious diseases or perhaps with a questionnaire assessing the quality of life after receiving a particular treatment. Often these longitudinal measures are incomplete or may be prone to measurement error. These measurements are also important because they may be predictive of survival. Therefore

methods which can model both the longitudinal and the survival components jointly are becoming increasingly essential in most cancer and AIDS clinical trials. In this part of the session, we will give a detailed development of joint models for longitudinal and survival data, and discuss Bayesian techniques for fitting such models. Examples from cancer vaccine trials will be presented.

Session 4. Bayesian Model Assessment in Survival Analysis

The scope of Bayesian model comparison is quite broad, and can be investigated via Bayes factors, model diagnostics and goodness of fit measures. In many situations, one may want to compare several models which are not nested. Such comparisons are common in survival analysis, since, for example, we may want to compare a fully parametric model versus a semiparametric model, or a cure rate model versus a Cox model, and so forth. In this session, we will discuss several methods for Bayesian model comparison, including Bayes factors and posterior model probabilities, the Bayesian Information Criterion (BIC), the Conditional Predictive Ordinate (CPO), and the L measure. Detailed examples using real data are presented, and computational implementation is examined.

Reference Book

J.G. Ibrahim, M.-H. Chen, and D. Sinha (2005), *Bayesian Survival Analysis*, Springer-Velag, Second Printing.
Website: http://www.stat.uconn.edu/~mhchen/survbook

Course 6: Statistical Methods in Bioinformatics (Whole Day Session)

Professor Jun Liu (Harvard University) will teach the short course about bioinformatics. A substantial core of computational biology (or bioinformatics) methods has been developed during the past three decades to meet the need of biological scientists for data storage, data retrieval, and data analysis. The databases of DNA and protein sequences contain millions of sequences, many completed genomes, and more are coming rapidly. DNA microarray data are being produced at a phenomenal speed. Protein arrays are being developed. High throughput structural data are being produced. Analysis of these data using bioinformatics tools has played a key role in several recent advances and will play increasingly important roles in future biomedical researches.

A main problem that motivated early research in computational biology is protein sequence analysis. Recently, because of the dramatic increase in many types of biological data due to the human genome project and other high-throughput projects, the scope of bioinformatics research has been extended to embrace diverse topics such as microarray analysis, protein classification, regulatory motif analysis, RNA analysis etc.

The sheer amount and variety of the molecular biology data have already presented a major challenge to all quantitative researchers. A distinctive feature of these data, be they microarray images, DNA sequences or protein structures, is that there is a large body of biological knowledge associated with them. This makes standard data mining or statistical analysis tools less effective. Incorporating relevant scientific knowledge into the development of statistical or computational analysis tools is the key to success.

This short course is intended to provide coverage of some key developments of bioinformatics with an emphasis on topics of recent interest. Topics include: pair-wise sequence analysis, local alignment, dynamic programming, BLAST, multiple sequence alignment, Gibbs motif sampler, gene regulation, hidden Markov models, context-free grammars, protein structure analysis, comparative genomics, model-based microarray analysis, clustering methods for microarrays, phylogenetic trees, etc.

Course 7: Statistics Using SAS Enterprise Guide (Whole Day Session)

Ms. Sue Walsh from the SAS Institute will provide a hands-on training. Students in this course will learn Enterprise Guide, a thin-client interface to the SAS System that provides transparent access to data, point-and-click usability, a customizable user interface, and easy export of results to other software applications . This workshop will introduce Enterprise Guide to explore and analyze data and then use the output to write reports and give presentations. Topics covered will include queries, one-way frequency tables, graphing, ANOVA, and logistic regression. Attendees will receive *Introduction to SAS Enterprise Guide for Biostatisticians and Epidemiologists* Course Notes.

Course 8: Pharmacokinetic-Pharmacodynamic Principles for Modeling and Simulation Based Drug Development (Whole Day Session)

Dr. Marc Gastonguay (Metrum Research Group) will cover principles of pharmacokinetic-pharmacodynamic modeling, including compartmental models, direct, indirect and physiologic exposure-response relationships, non-stationary pharmacodynamics, population PK-PD methods, Monte Carlo clinical trial simulations, and the application of these methods to support drug development.

ICSA 2006 Applied Statistics Symposium
Student Awards & Travel Grants

The 2006 Annual ICSA Applied Statistics Symposium will be held during June 14-17, 2006 at the University of Connecticut, Storrs, Connecticut, USA. The Symposium will sponsor the Student Awards and Travel Grants. The main purpose of the award is to encourage student members of ICSA to participate and present their research work at this annual meeting.

Qualifications: The student must be an ICSA member (or join at the time of manuscript submission), a degree candidate in any term during the academic year 2005-2006 at an accredited institute and be able to register and present the work at the 2006 symposium.

Manuscripts should be prepared double spaced using Biometrics or JASA guidelines for authors. They must be no more than 20 pages in length exclusive of tables and figures. Use one-inch margins and no smaller than 12 point type. The work must be relevant to applications in a variety of fields including biomedicine, business, etc. The manuscript may be co authored with a faculty adviser and/or a small number of collaborators, although the student must be the first author.

Review and Selection Process: The members of Student Award Committee and J. P. Hsu Memorial Scholarship Committee will receive blinded copies of the submitted manuscripts from the Committee Chairs and review them based on the following criteria:

- The manuscript should be well motivated by an application relevant to the specific field(s).
- The methodology developed should be applicable to the motivating problem. Inclusion of an application of the proposed methodology to a particular study will be favorably considered.
- Organization and clarity of the presentation will be considered as well.

Up to 3 award winners will be selected by the Awards Committees chaired by Heping Zhang and Fred C. Djang. Each winner will receive a certificate, $400, and tuition for one short course of his/her choice. Winners will be notified by April 24, 2006.

Submission of Manuscripts: Manuscripts should be received and postmarked no later than April 1, 2006.The submission should include:

- A cover letter
- One complete title page with author(s), institutional affiliation, mailing address, phone/fax numbers and email address
- Five copies of the manuscripts with only a title, but no information on authors or affiliation, on the first page
- Two copies of abstract
- Two copies of the ICSA membership application for non-members

Membership forms can be downloaded from http://www.icsa.org. All materials should be mailed to:

Professor Heping Zhang (heping@med.yale.edu)
Department of Epidemiology and Public Health
Yale School of Medicine, Yale University
60 College Street
New Haven, Connecticut 06520-8034 USA.

International Chinese Statistical Association
Profit and Loss

January 1, 2005 through Dec 31, 2005

Balance, Dec 2004	64,625.13
Income	
2004 interest income (included in 2004 tax filing)	156.90
2005 interest income from CD	886.80[1]
Short course income from Applied Symposium	6704.33
Membership Dues	5100.00[2]
Miscellaneous	84.73
Total Income	12932.76
Expense	
Miscellaneous	
Member dinner at 2004 JSM	655.00
Member dinner at 2005 JSM	1457.55
Board meeting & committee lunch at JSM 2005	482.62
Member services	123.96
Total Miscellaneous	2719.13
Postage and Delivery	
January Bulletin	1738.90
July Bulletin	2849.69
Book/journal donations	1534.00
Total Postage and Delivery	6122.59
Printing and Reproduction	
January Bulletin	2470.00
July Bulletin	4120.00
Total Printing and Reproduction	6590.00
Professional Tax Services	612.25
Total Expense	16043.97
Net Ordinary Income	-3110.21
Other Income/Expense	0
Net Other Income	0
Net Income	-3110.21

International Chinese Statistical Association
Balance Sheet

January 1, 2005 through Dec 31, 2005

ASSETS	
Checking/Savings	
Checking	20627.12
Savings-Money Market	40886.80[1]
TOTAL ASSETS	61513.92
LIABILITIES & EQUITY	
Equity	
Opening Balance Jan 1, 2004	64625.13
Net Income	-3111.21
Total Equity	
TOTAL LIABILITIES & EQUITY	61513.92

Note:
1. Estimation based on sum of monthly interest. Might be slightly different from Form 1099-INT.
2. Including only checks deposit before Jan 01, 2006.

Submission Guidelines for ICSA Bulletin

Articles

The International Chinese Statistical Association (ICSA) Bulletin welcomes the submission of articles by our members. Articles submitted should be written in English. The contents should be aimed at the general reading.

Articles should be submitted electronically in Microsoft Word documents. Files with font size of 11 or 12 (preferred) are preferred. Leave ¾ inches of blank space on each margin in regular or letter size pages (8.5 inches in width by 11 inches in height). If pictures are included in a document, then corresponding JPG files are required and must be sent separately. Without the JPG files, their publication quality may not be assured.

Submission deadlines are December 1 for the January issue, and June 1 for the July issue. Articles received after the deadline may be published in the following issue of Bulletin.

Reports or Announcements

The submission guidelines of reports or announcements are the same as the articles. Editable files in Microsoft Word are preferred. If PDF files are sent, be sure that the margins or fonts are met as required in the ***Articles.***

Advertisements

The ICSA Bulletin welcomes the submission of advertisements related to the profession of Statistics. The fee charge is $225 for a half page, $325 for a full page, $350 for a color page (in front-inside, bottom-inside, or bottom-outside pages). If you have questions or advertisement opportunities, please contact the Advertising Manager or Editor-in Chief.

Questions

Please submit your questions to the Editor-in-Chief by email: tkao@usuhs.edu

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

泛華統計協會

2006 APPLIED STATISTICAL SYMPOSIUM REGISTRATION

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

Step 1 - Personal Information

English Name: _____ ☐ Mr. ☐ Ms. ☐ Mrs. ☐ Dr. ☐ Prof.

Chinese Name: _____ Gender: ____ Phone: _____

Address: _____ Fax: _____

_____ Email: _____

City: _____ State: ____ Affiliation: _____

Country: _____ Postal Code: ____ Category: ☐ Industry ☐ Gov ☐ Academic

Do you require any special accommodations to participate? _____

Are you a presenter? ☐ Yes ☐ No ☐ Overhead ☐ Slide Proj. ☐ Powerpoint ☐ Other: _____

Step 2 - Symposium Registration

Please check the appropriate box below. The fee includes breakfast, lunch, and coffee breaks for June 15, 16, and 17.

Before April 30, 2006		After April 30, 2006	
☐ Member	$ 160	☐ Member	$ 180
☐ Non-Member	$ 200	☐ Non-Member	$ 220
☐ Student Member	$ 70	☐ Student Member	$ 90
☐ Student Non-Member	$ 90	☐ Student Non-Member	$ 110

☐ I will not be attending the Symposium, but will register for a short course.

registration fee

$

Step 3 - ICSA Membership

Non-Member symposium registrants will receive a one year membership. For new membership or renewals please print the Membership Application Form available at www.icsa.org and mail it with this Registration Form.

ICSA Member Attendees, please renew your membership	
☐ Annual Regular Membership	$ 40
☐ Lifetime Permanent Membership	$ 400
☐ Annual Student Membership	$ 20

☐ My membership is up to date already - no need to renew

membership fee

$

Step 4 - Short Course Registration (Wednesday, June 14)

Short courses are optional and require a separate registration fee. The symposium registration fee is not required when attending only a short course. Lunch and coffee breaks are included in the fee. Please select the short course you will attend.

	Before April 30, 2006	After April 30, 2006
1. Statistical Analysis of Financial Data Prof. Yazhen Wang, *University of Connecticut* *9am - 12:30pm*	☐ Non-Student **$160** ☐ Student **$30**	☐ Non-Student **$185** ☐ Student **$40**
2. Contributions to Discrete Distributions Prof. Daniel Zelterman, *Yale University* *1:30pm - 5pm*	☐ Non-Student **$160** ☐ Student **$30**	☐ Non-Student **$185** ☐ Student **$40**
3. Design and Analysis of Dose Response Clinical Trials Dr. Naitee Ting, *Pfizer Global Research & Development* James MacDougall, *Bristol-Myers Squibb* *1:30pm - 5pm*	☐ Non-Student **$160** ☐ Student **$30**	☐ Non-Student **$185** ☐ Student **$40**
4. Active Controlled Clinical Trials Dr. Yi Tsong, *CDER, Food and Drug Administration* *9:00am - 5pm*	☐ Non-Student **$300** ☐ Student **$50**	☐ Non-Student **$350** ☐ Student **$60**
5. Bayesian Methods for Survival and Longitudinal Data Prof. Joseph G. Ibrahim, *University of North Carolina* Prof. Ming-Hui Chen, *University of Connecticut* *9am - 5pm*	☐ Non-Student **$300** ☐ Student **$50**	☐ Non-Student **$350** ☐ Student **$60**
6. Statistical Methods in Bioinformatics Prof. Jun Liu, *Harvard University* *9am - 5pm*	☐ Non-Student **$300** ☐ Student **$50**	☐ Non-Student **$350** ☐ Student **$60**
7. Statistics Using SAS Enterprise Guide Ms. Sue Walsh, MBA, MS, *SAS Institute Inc.* *9am - 5pm*	☐ Non-Student **$300** ☐ Student **$50**	☐ Non-Student **$350** ☐ Student **$60**
8. Pharmacokinetic-Pharmacodynamic Principles for Modeling and Simulation Based Drug Development Dr. Marc R. Gastonguay, *Metrum Research Group LLC* *9am - 5pm*	☐ Non-Student **$300** ☐ Student **$50**	☐ Non-Student **$350** ☐ Student **$60**

short course fee

$

Step 5 - Transportation

Complimentary shuttle transportation is available from and to Bradley International Airport and Union Station in Hartford, CT. Coach bus transportation has also been arranged for an excursion to Mohegan Sun Resort & Casino on the evening of Thursday, June 15. Please reserve your transportation services as applicable below:

☐ **Yes, I will require transportation to Storrs upon arrival**

Shuttle From: ☐ Bradley Airport ☐ Union Station

Arrival Date: _____ Arrival Time: _____

Airline/Flight#: _____ # of Travelers: _____

☐ **Yes, I will require transportation to Hartford on departure**

Shuttle To: ☐ Bradley Airport ☐ Union Station

Depart Date: _____ Depart Time: _____

Airline/Flight#: _____ # of Travelers: _____

☐ Yes, I will attend the evening excursion to Mohegan Sun Resort & Casino on 6/15. There will be a total of _____ travelers.

Step 6 - Lodging

Please review the conference website for a detailed description of the lodging options and indicate your selections below:

☐ **No On-Campus Lodging Required**

☐ **Nathan Hale Inn** *(Reservations must be made directly with the hotel by calling 860-427-7888.)*

☐ **University Residence Hall** *(Reservations are made using this form. Payment is due upon registration.)*

If you are traveling to Storrs alone, please select option A or option B:

A ☐ Conference Single (private bedroom w/ one bed, in a suite with shared bath **$55 per night**)

B ☐ Conference Double (shared bedroom w/ two beds, shared bath **$38 per person per night**)

For option B, indicate roommate (or one will be assigned): _____

If you are traveling to Storrs with family or a companion, please select option C or option D:

C ☐ Family Double (shared room, two beds, shared bath **$76 per night**)

D ☐ Family Suite - (Suite with four beds, shared bath **$110 per night**)

For option C or D, please list names of family / companions:

_____

Arrival Date: _____ Departure Date: _____ # of Nights: _____

total lodging due

$

Step 7 - Banquet Dinner

A banquet dinner and guest lecture by Dr. Henry Lee will be held on the evening of Friday, June 16. The cost of this optional event is not included in the registration fee and must be paid for separately for participants and guests. Please indicate below if you will participate in this event:

☐ Yes, I will participate in the banquet

Number of Adults Attending **($30 each):** _____ Children under 12 Attending **($15 each):** _____

banquet fee

$

Step 8 - Total Conference Payment

Please enter / verify the appropriate fee amounts based on your selections:

Total Amount Due

	+		+		+		+		+		=	
												$
Symposium		Membership		Short Course		Lodging		Banquet		ICSA Donation		

Please print and send this completed registration form with check payable to "ICSA 2006 Symposium" to:
Lynn Kuo, Treasurer, ICSA 2006 Symposium, Department of Statistics, University of Connecticut, 215 Glenbrook Road, U-4120, Storrs, CT 06269-4120.

Cancellation Policy: For cancellation of any part of your registration, the following refund schedule will apply.
100% refund before April 30, 2006; 80% refund between April 30 and May 15, 2006; no refunds issued after May 15, 2006.

Print Form