泛華統計協會

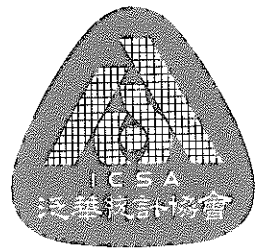
會刊

International Chinese Statistical Association

Website: http://icsa.org

Bulletin

July 2002



編者的話:

會刊是我們會員的主要交流園地，預計每年在一月及七月發行兩期，希望各位踴躍賜稿，文章以一至二頁爲主，須用中文繁體字或英文書寫，文章性質以一般性非專門學術的文章爲主，以前或本期會刊內的各篇短文都是很好的範例，稿件如採用，我們希望能由作者安排打字，完稿的上，下，左，右邊 (margin) 至少要有四分之三英吋，頁碼離底邊二分之一英吋，打字打在 8" x 11" 的白紙上。爲統一起見，若以英文書寫，請用 Microsoft Word 打字，中文繁體字請用 Microsoft Word with Valupack Fareast feature 打字。稿件的截止日期是六月十五日及十二月十五日。截止日期後收到的將列爲下一期的稿件。

刊內付有本會的申請表 (application form)，其中會員動態內的著作 (publication) 以一年內的新作品爲限。

從 1994 年度起本會酌收徵才廣告費一頁 U.S.$200 或半頁 U.S.$120。

對於以上的一些構想，如果您有任何建議，請與泛華協會執行長莊易 (地址見下) 聯絡，以期這份刊物更爲完善。

Website: http://www.icsa.org

I.C.S.A. c/o Yi Tsong, Ph.D.
13215 lazy Glen Lane
Herndon, VA 22071
U.S.A.

EXECUTIVES AND MEMBERS OF THE COMMITTEES OF ICSA 2002

EXECUTIVES

President:	William W. S. Wei (2002)
Past President:	Chao Agnes Hsiung (2002)
President-elect:	Zhiliang Ying (2002)
Executive director:	Yi Tsong (2001-03)
Treasurer:	H. M. James Hung (2001-03)

BOARD OF DIRECTORS

Ngai Hang Chan (2001-03), Chen-Hsin Chen (2001-03), Rong Chen (2002-04), Jianqing Fan (2000-02), Agnes Hsiung (2000-02), Mei-Ling Lee (2001-03), Guo-Ying Li (2001-03), Ker-Chau Li (2000-02), Zhaohai Li (2002-04), Kar K. Lin (2000-02), Jun Shao (2000-02), X. Don Sun (2001-03), Naitee Ting (2002-04), Mei-Cheng Wang (2000-02), Sue-Jane Wang (2002-04), William W.S. Wei (2001-03), Zhiliang Ying (2002-04), Heping Zhang (2002-04), Frank Shen (2000-02, Biometrics Section Representative)

STANDING COMMITTEES

Program Committee:
Wei-Yann Tsai (Chair 2002, member 2002-2004), Hubert J. Chen (2002-03), Rony Chen (2002-03), Xiao Li Meng (2002-04), Jiann-Ping Hsu (2002-03), W.K. Li (2002-07), Jia-Yeong Tsay (2002), Zhiliang Ying (2002)
Term of reference: to recommend conference and symposium sites, including candidates for their chairs; to recommend general policy for all meetings, subject to approval by the Board of Directors

Finance Committee:
H.M. James Hung (chair 2001-03), Xiu Chen (2001-03), Wei-Ying Yuan (2001-03)
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

Nominating and Election Committee:
Naitee Ting (chair 2002, member 2002-03), Jeff C. F. Wu (2002-03), Jen-Pei Liu (2001-2002), Heping Zhang (2002)
Term of reference: to nominate the candidates for President-elect and members of the Board of Directors

Publication Committee:
James J. Chen (Chair 2002, member 2000-02), I-Shou Chang (2001-03), Jun Shao (2002-04), Sue-Jane Wang (Bulletin), Ker-Chau Li, Yi-Ching Yao (Statistica Sinica), Yi Tsong (ex-officio)
Term of reference: to oversee the publication policy of the Association and make recommendations to the Board of Directors

Constitution Committee:
Frank Shen (Chair), Shein-Chung Chow, 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:
Tzu-Cheg Kao (Chair 2002, member 2000-02), Rongdean Chen (2001-03), Chong Gu(2000-02), Zhaohai Li (2000-02), Xufeng Niu (2000-02), Ming Tan (2001-03), Heping Zhang (2001-03), Ling Chen (2002-04), Wai-sum Chan (2002-04, Hong Kong), Chen-Hsin Chen (2002-04, Taiwan), Guo-Ying Li (2002-04, China)

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

Fundraising Committee:
Alice Hsuan (Chair 2002, member, 2001-03), Jianping Dong (2002-02), Kuang-Chao Chang (2002-02)
Term of reference: to consider fundrasing drives through individuals and corporations

Public Relations Committee:
Yi Tsong (Chair, 2002, member 200-02), Naisyin Wang (2000-02), Shi-Yong Feng (China), Sik-Yum Lee (Hong Kong), Lung-An Li (Taiwan)
Term of reference: to contact the news media and publicize ICSA activities; to serve as a liaison between ICSA and other professional organizations such as ASA, Biometric Society for joint activities

Awards Committee:
Lynn Kuo (Chair 2002, member 2002-02), Wen-Jang Huang (2001-03), Zhaohai Li (2001-03), Jane-Ling Wang (2002-04), Ming Tan (2000-02), Sue-Jane Wang (2002-04)
Term of reference: to accept, evaluate, and recommend nominations for ICSA various awards

Communication Committee:
Rong Chen (Chair 2002, member 2002-04), Don Sun (Web), Hubert Chen (Listserv)
Term of reference: to evaluate the database and use of internet

Applied Statistics Symposium Committee:
William W. S. Wei (Chair), Danny Chaing, Ivan Chan, George Chao, Yusong Chen, Alice Hsuan, Lee Huang, Frank Shen
Term of reference: to organize the Applied Statistics Symposium, 2002

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:
Wei-Yann Tsai (Chair 2002, member 2002-2003), Hubert J. Chen (2002), Zhiliang Ying (2002)
Term of reference: to plan, coordinate and arrange the August annual meeting, 2002

Archive Committee:
Yi Tsong (Chair 2002, Smiley Cheng, Shein-Chung Chow, Nancy Lo, Naitee Ting
Term of reference: to plan and implement electronic archive for the Association

Strategic Committee
Chao Agnes Hsiung (Chair 2002), 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, Georhe Tiao
Term of reference: to plan long-term strategies for the Association

BIOMETRICS SECTION (2002)

H. M. James Hung (Chair), Wei-Chung J. Shih (past chair), Jen-Pei Liu (Chair-elect), Shou-en Lu (secretary), Gang Li (treasurer), Frank Shen (ICSA Representative 2000-02)

EXPRESS YOUR OPINION .....

Dear ICSA Members,

The upcoming 2003 applied statistics symposium (to be held at San Diego, California) and the 6th international conference of 2003 are sponsored by the ICSA. We'd like to notify you ahead of time and encourage your involvement by contacting the chairs of the corresponding events (details see announcement) or by sharing your research findings with the members. Your suggestions/comments are welcomed. More details inside .....

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GET INVOLVED IN NEXT ISSUE .....

Statistics' Delight/ 統 計 趣 聞
Controversial statistical
Issue—Flexible design

Get involved in the next issue by email your articles to the Editorial Board

Editor's Page

ICSA's Eminent Tradition

July 04, 2002

In this issue, we highlight the success of the 2002 ICSA Applied Statistics Symposium headed by Dr. William Wei, our President. Instead of using the usual East Coast locations, our program committee has tried new locations since last year from Chicago, Illinois (2001) to Philadelphia, Pennsylvania (2002) and the 2003 symposium will take place in San Diego, California. Experiences are abundant. Following the report of the Applied Statistics Symposium, keynote speeches presented by Dr. Robert T. O'Neill and Dr. George W. William are also published for members who could not attend the meeting. We reserve a corner for discussion on clinical therapeutic bridging studies - one of the "controversial statistics issues." And, Dr. Timothy T. Chen, former president in 1999, contributed an article on 'If I could do it all over again,' which provides important mentoring stories and may serve as an excellent reference for some members who may have just started their statistical careers. For interested readers, be sure to enjoy our new puzzles in the Statistics Delight Section.

The use of pharmacogenetics/pharmacogenomics (PG) in drug development is increasing and its use has tremendous potential to have a positive impact on public health and health economics. This year, in addition to our regular symposium, ICSA is also co-organizing a conference entitled "Symposium on Biomedical Technology Development" to be held at the University System of Maryland, Shady Grove Center, Maryland. The symposium date is September 28–29, 2002. Meeting announcement and registration form can be found in the announcement section and will be posted on our website.

As some of you may know, this is the last issue during my three-year term as the Editor-in-Chief, and I almost feel like saying, "WHEW!" it's been such a run. As we inherited the baton from the former editing team at a full sprint, I feel that all of the wonderful colleagues I have worked with felt that we should do nothing less than try our best to continue that sprint, which I am sure the next team will enthusiastically continue. With members' enthusiasm and the hard work of my colleagues, I am thankful for the rewarding experience I have had reviewing all of the wonderful contributions from all you readers for the ICSA bulletin. It is of such acclaim, we often hear praising comments not only at professional meeting gatherings but also through email responses. We are delighted to receive the strong support and have really enjoyed this service to members of the ICSA.

Lastly, I have put together an 'Editorial Working Committee' page in this issue to introduce to you the members of our editorial committee whom I greatly enjoyed working with and include a short paragraph they'd like to share with ICSA members.

Sue-Jane Wang

Editor-in-chief, 2000-2002

MESSAGE FROM THE PRESIDENT

June 30, 2002

Dear ICSA Members:

The success of an organization comes from the sustained dedication of its members. This is especially true for a non-profit organization like ICSA. Many of our members spend their evenings, weekends, and holidays working for ICSA without any compensation. For example, because of the effort and many personal sacrifices of Editor-in-Chief, Sue-Jane Wang, our members can enjoy the wonderful ICSA Bulletin. This bulletin has a size equivalent to AMSTAT NEWS but with much wider and richer coverage. During the past three years, while we were enjoying our Christmas holidays with our families, Sue-Jane was working in her home office, calling people for over-due reports, and editing articles for the final printing of the Bulletin. She completes her three-year term as Editor-in-Chief at the end of this year. She really deserves a good break. We give her our salute and thank her for the exceptional work she has done.

It has been nine years since the ICSA Constitution and By-Laws were revised. To meet the Association's changing needs, the Constitution Committee (Shein-Chung Chow, Chien-Pai Han, and Frank Shen (chair)) carefully reviewed the Constitution and By-Laws and proposed several changes, published them in the January 2002 issue of the Bulletin, and invited comments from members. At the June 7 meeting, the Board approved the revisions after careful discussion. The two most important changes were the responsibilities of the Program Committee and the Finance Committee. The Program Committee is the only standing committee of ICSA that deals with meetings. However, under the previous version of the Constitution and By-Laws, it plays no role in any ICSA related programs other than the August annual gathering at the Joint Statistical Meetings. Under the approved revision, the Program Committee will assist the Annual Meeting Committee in planning the annual meeting as well as recommend symposium and conference sites, including candidates for their chairs. The Committee also recommends general policy for all meetings. In the same spirit, the Finance Committee will not only deal with income, expenditures, and budget, but most importantly, it will also have the responsibility of long-term financial planning, including the investment of the Association's assets.

The world is changing and new technology is developing quickly. To keep up with these new developments, we need to keep learning during our lifetime. To provide our members with the opportunity of continuing education, we have offered short courses in the annual ICSA Applied Statistics Symposium. The Association should continue the program and offer courses in even more diverse areas. In addition, under the editorship of Sue-Jane, the ICSA Bulletin published many excellent introductory and review articles on various topics. For example, the January 2002 issue of the ICSA Bulletin contained very interesting articles in pharmacogenomics and missing data problems. I hope that our members take full advantage of these offerings.

Because of new technology, e-mail and the world wide web have become the most common and efficient communication tools. They are also the best sources for searching for information. Many organizations have actually stopped using

paper communication and rely solely on e-mail and the web for communication and announcements. This includes conference announcements, registration, and elections. For example, beginning this year, the Joint Statistical Meetings, where many of our members also actively participate, is no longer sending out a registration booklet. People interested in attending have to go to the website of participating societies to submit online registration forms or download the required forms and mail them in. ICSA is also working on this communication update. I sincerely request that all our members visit the Association's website (http://www.icsa.org) and update their membership information regularly, especially e-mail addresses, so that we can start to communicate with each other more efficiently.

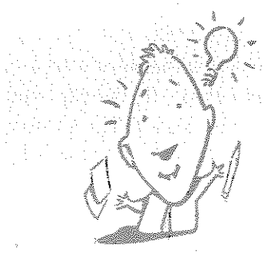
The ICSA is an international statistical and non-profit organization registered in the US. The Association is organized and operated for educational, charitable, and scientific purposes without regard to race, creed, color, sex or nationality. To expand the scope and impact of our Association, one of my goals as president is to attract more non-Chinese members to the Association. After the keynote speeches at the 2002 ICSA Applied Statistical Symposium, I briefly introduced the Association and pointed out the benefits of being a member to the conference participants. I am pleased to report that we had many Chinese and non-Chinese colleagues joining the Association afterward. We warmly welcome them.

The Association holds two membership meetings each year, one at the ICSA Applied Statistical Symposium and one at the Joint Statistical Meetings. The symposium this year was held in greater Philadelphia from June 6–8. There were 265 participants, a record-breaking number, and about one hundred members attended the membership meeting. The Joint Statistical Meetings this year will be in New York City from August 11-15. Professors Wei-Yann Tsai and Zhiliang Ying are organizing the August meeting. Please refer to the enclosed announcement for more details. I look forward to seeing you there. Have a pleasant and productive summer.

William Wei
President

Special announcement from The Editorial Board

- The next Bulletin issue will be prepared and led by the to-be-elected Editor-in-Chief.
- The Editorial Board 2000-2002 would like to thank all contributors and readers for your support.
- We encourage your active involvement in the ICSA Bulletin. Every effort counts.



FROM THE EXECUTIVE DIRECTOR

Dear Friends:

No one can argue about the fact that ICSA is a very successful association now. The association is managed with a system. Our official journal Statistica Sinica enjoyed successful recognition year after year. Our Bulletin has evolved into a periodical with high readability with a group of energetic editors with new ideas. Our International conference blends traveling fun with knowledge sharing so successfully. Our symposium enjoys steady growth every year. This year we have over 200 participants. Does anyone remember those days with about 70 participants? ICSA Applied Stat Symposium today attracts outstanding presenters in various fields.

Friends, at the time we enjoy the fruit of success, we are also looking forward to the new challenges.

In the 2002 July issue, I identified three priority projects, accounting and tax report, homepage and web service, and electronic archiving of documents. In accounting and tax report, very fortunately, James Hung (ICSA treasurer) and I found a very experienced CPA in Ms. Li-Ming Li of Rockville. With James' effort and close working relationship with Ms. Li, the accounting and tax report is under excellent control. With the expertise and effort of our Web Master Dr. Don Sun, our homepage becomes very impressive. However, electronic archiving had not exactly enjoyed much improvement. I will try to improve it.

In order to keep up with the pace of this new age of electronic communication, we need to meet the new challenges and take advantage of what the technology offers. These are a few more projects that I believe we need to work on.

1. Establish an updated e-mail system—With the ever-increasing cost of postage and labor, and the time needed to handle the mails, mailing is not the first choice as the format of information distribution. Many of the information distributions will be replaced by e-mailing in the near future. I was quite embarrassed to find out that almost one- to two-third of our e-mail addresses were out of date during Prof. George Tiao's campaign for ASA president. Remember, your updating of e-mail address is crucial to the success of ICSA's information distribution.
2. Actually, the important reason of the bounced back e-mails is that there are quite a few once members who didn't renew the membership. Among the 1500 plus entries in our directory, less than half updated their memberships. The annual reminder at the end or beginning of the year seems didn't serve the purpose each year. I don't quite agree with the suggestion of sending more reminding letters through the year. I believe that with good and useful products, the customers will come. Hence I am looking forward to create more membership only services such as e-journal and bulletin, electronic chat room on controversial statistical issues, etc. All these service will take time and effort to develop. But we have talented and energetic members handle the problem.
3. The annual voting has always been time pressing because of the time and effort required for printing and mail handling. We will be investigating the possibility of electronic voting once we have a healthy e-mail system.

I am looking forward to hear from you on suggestions and proposals to improve the services and the association.

Yi Tsong

MINUTES OF 2002 JUNE ICSA MEMBERSHIP MEETING

DoubleTree Hotel Guest Suites, Plymouth Meeting, PA, June 8th, 2002

Time: 5:30 PM-6:15 PM
Chair: William Wei (President)
Minutes: Yi Tsong
Attendees: About 70 ICSA Members

1. President Report

Prof. William Wei made announcement that the 2002 August Membership Meeting will be held on August 13 at Hilton Hotel in New York

Prof. William Wei congratulated and thanked the participants of the successful Symposium. He introduced the members of the Symposium Program Committee, Working Committee members and student helpers and expressed sincere thanks for their commitment and dedicated efforts. He announced proudly that the number of attendees was over 200 this year.

The president reported also that Prof. George Tiao, the founding father of ICSA was at the symposium earlier (which means his symposium attendance record is 100%) and left earlier for a meeting at Atlanta Georgia. He mentioned that Prof. George Tiao expressed his sincere thanks to the members for their efforts to support his campaign for ASA presidency. George is extremely happy for the turnout of the election result that he lost to Prof. Efron with a narrow margin of 43% to 56%. He wanted everyone to accept the result positively as a very successful indication for ICSA member planning to run for major ASA positions in the future.

Prof. William Wei congratulated three ICSA members, Professors Joseph Gastwirth (Chair-elect, Section on Nonparametrics), Dennis Lin (Chair-elect, Section on Physical and Engineering Sciences) and Xiao-Hua Zhou (Chair-elect, Section on Statistics in Epidemiology) for their successes in elected to the positions in ASA.

2. Honor ceremony

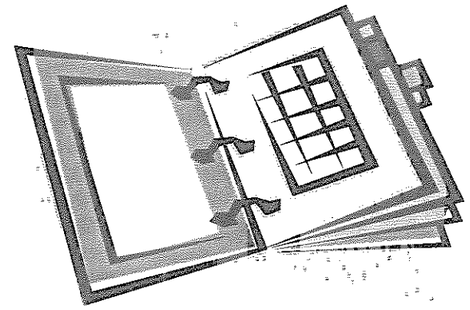
The following honors and certificates were given at the meeting,
The student Award and Travel Fellowships
ICSA Certificates of Appreciation and souvenirs for Keynote Speakers,
Drs. Robert O'Neill, George Williams and Plenary Speaker, Dr. Gordon K.K. Lan
ICSA Certificates of Appreciation for the ICSA Symposium Corporate Sponsors
ICSA Plaque for the 2001 ICSA Applied Statistics Symposium Program Committee
ICSA Certificates of Appreciation for the members of the 2001 ICSA Applied Statistics Symposium Program Committee, Planning Committee and Local Service Committee

3. Announcement of future ICSA Applied Statistics Symposiums

Dr. Nancy Lo announced that the 2003 ICSA Applied Statistics Symposium is to be held at University of San Diego, California with the preliminary program to be published in the July issue of ICSA Bulletin

Dr. Yi Tsong announced also that the Board of Directors approved that the 2004 ICSA Applied Statistics Symposium to be held at Washington D.C. Metropolitan Area.

Meeting was adjourned at 6:00 PM for Banquet.



Report on the ICSA 2002 Applied Statistics Symposium

William W.S. Wei
Held at Plymouth Meeting in Greater Philadelphia, Pennsylvania

The ICSA 2002 Applied Statistics Symposium was held from June 6 to 8, 2002, at Plymouth Meeting in Greater Philadelphia, Pennsylvania. The theme of the symposium was the leading edge of statistics in health sciences. Under this theme, we invited two keynote speakers, Dr. Robert O'Neill, Director of Office of Biostatistics, CDER, FDA, and Dr. George Williams, Vice President of Biostatistics and Programming, Pharmaceutical Research Institute, Bristol-Myers Squibb Co., and Vice President of ASA. They presented our symposium audience with two different but related views: one from the regulatory point of view and one from the industry point of view. Dr. Gordon Lan, Pfizer Inc., was our other plenary speaker who gave an excellent talk on adaptive design and analysis.

The first day of the symposium consisted of short courses. There were a total of 95 people registered for these four very interesting and stimulating courses: Design Considerations for Positive Late Phase Confirmatory Trails by Dr. Irving Hwang; Active Control Non-Inferiority Studies and Adaptive Analysis Methods in Clinical Trials by Dr. Sue-Jane Wang and Dr. James Hung; Statistical Approaches in Pharmacogenomics by Dr. Kim Zerba, Dr. Shu-Pang Huang and Dr. Frank Shen; and Advanced Log-linear Models for Categorical Data with GENMOD by Prof. Daniel Zelterman.

During the next two days of the conference, technical sessions were held on various topics, including statistical considerations in evaluating patient reported outcomes, statistical data mining in early drug discovery, design and analysis of cancer trials, multiple imputations of missing values, issues and advancement in pharmaceutical statistics, statistical applications in genomic research, financial econometrics, regulatory issues in planned interim analy-

sis, statistical issues in design and analysis of microarray data, non-parametric methods in longitudinal analysis, advancement of computer assisted trial design in drug development, statistics issues in pre-clinical research, design and analysis of active control non-inferiority trials, exact conditional inference for categorical data, statistical modeling, large data sets, and analyses of clinical data and specially structured data. Speakers included many world-renowned scholars, young researchers, and Ph.D. students.

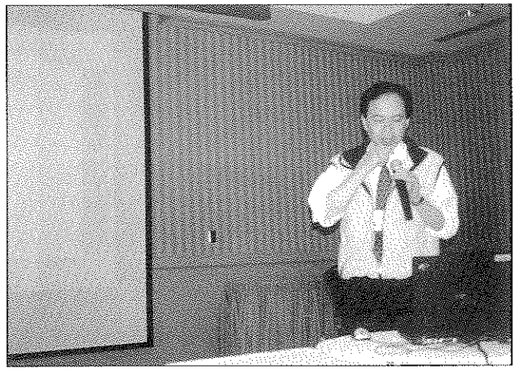
The symposium would be incomplete without the banquet and karaoke. This important trademark of the symposium took place on Friday night at an excellent Chinese restaurant in the Philadelphia suburbs. The evening offered a delicious 10-course banquet. Judge Ida Chen, the first Asian American female judge appointed by the Governor of Pennsylvania to serve in the Court of Common Pleas in the Commonwealth of Pennsylvania and the first Asian American to be elected in a city-wide campaign, as a Judge of the Court of Common Pleas in Philadelphia, was our special invited banquet speaker. She gave a very inspiring talk on "Great Expectations." We were all deeply moved. Highlights of the evening also included music shows and songs performed by two outstanding musicians from the Philadelphia Chinese Opera Society and many wonderful singers from our symposium participants.

The symposium was truly a great success. We had a record-breaking number of 265 participants, many of whom were from overseas. Many attendees have personally conveyed to me how much they enjoyed the event and learned from the symposium. The process of organizing a successful conference is just like the process of raising a child. The only differences are that organizing a conference requires the effort of more than two people and it takes longer than nine months. The program committee was formed in October 2000 and started its monthly planning meetings in November 2001. I am very grateful to these dedicated committee members, including Danny Chaing, Ivan Chan, George Chao, Yusong Chen, Alice Husan, Francis Husan, Lee Huang, and Frank Shen. The symposium would not have been such a success without their dedication and sacrifices. I would also like to thank Chung-Kuei Chang, Yuning Liao, Wenjing Wang, and Brian Yan for taking photos for the symposium and Yue Chen, Shuwei Ma, Xiaoyan Qin, and Sha Xiao for helping with registration.

To encourage students to participate in professional meetings, we continue to offer student awards and travel fellowships. We thank the Student Award and Travel Fellowships Committee: Weichung J. Shih (Chair), Cun-Hui Zhang, and Zhiliang Yin, and congratulate this year's winners: Zhengjun Zhang, Jun M. Liu, and Yi-Chuan Zhao. We also thank our corporate sponsors AstraZeneca, Aventis Pharmaceuticals, Bristol-Myers Squibb Company, GlaxoSmith Kline, Johnson & Johnson PRD, Merck & Co., Novartis Pharmaceuticals, Organon Inc., Pfizer Inc., Purdue Pharrma, and Wyeth Consumer Healthcare. Their generous financial contributions support these student awards and many other programs in this symposium.

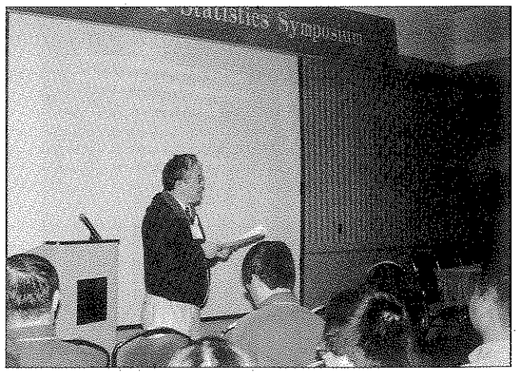
In closing, on behalf of the Committee, I wish to thank all short course instructors, session organizers, speakers, and participants for their contributions. Their efforts in choosing the right topics and selecting the right speakers to make outstanding presentations and conduct stimulating discussions have contributed greatly to the success of this symposium.

Program Committee—2002 ICSA Applied Statistics Symposium

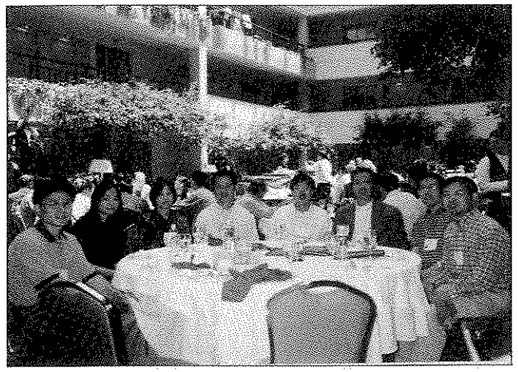


Plenary session speaker, Dr. Gordon Lan of Pfizer Inc.

Members of the symposium audience



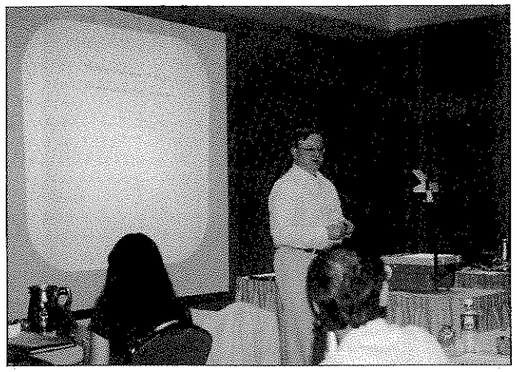
Dr. Jen-pei Liu, National Health Research Institutes, Taiwan



Lunch Break at the symposium

Banquet speaker, Judge Ida Chen, receiving a certificate and a small token of appreciation from the symposium chair, Prof. William Wei

Dinner Banquet



Dr. Daniel Zelterman, Yale University

Editorial Working Committee

Sue-Jane Wang, Ph.D.
U.S. Food and Drug Administration, Maryland, USA

With the growing population, life follows but a central limit theorem. Outliers, too small or too large, worst or best, etc. may be considered 'special' for a short while. Eventually, we live toward a bell-shaped world. "Harmonic mean" is in our heart.

3 6 7 1 4 5 0 2 3
9 1 2 3 1 6
7 8 4 3 0 2 1
5 5 9 9 3
6 0 7 3

C. Andy Tsao, Ph.D.
Nationl Dong Hwa University, Taiwan.

"We are faced throughout our lives with agonizing decisions, moral choices... But we define ourselves by the choices we have made. We are, in fact, the sum total of our choices. Events unfold so unpredictably, so unfairly. Human happiness does not seem to have been included in the design of creation… And yet, most human beings seem to have the ability to keep trying and even to find joy from simple things like their family, their work and from the hope that future generations might understand more." (Crimes and Misdemeanors, Woody Allen)

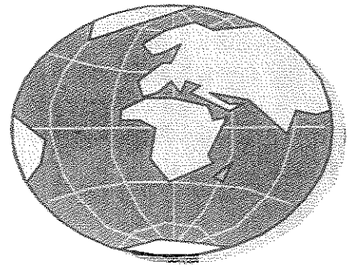
Hailiang Yang, Ph.D.
The University of Hong Kong, China

As a teacher, I want to offer my students some insight into all the interesting aspects of actuarial science. However, when not teaching, I also enjoy research and receive great pleasure out of new discoveries and being able to contribute something to the world of science.

Kao-Tai Tsai, Ph.D.
Aventis Pharmaceutical Inc.

Everyone should know as much as statisticians do but nobody should ever call himself/herself a statistician.

Statisticians are almost always at the supporting role and, therefore, are almost always under-appreciated. (Try to work with Mentally Damaged M.D. and you will know...)



Teach your children statistics but never ever encourage them to follow your footstep unless.....

Hung-Ir Li, PhD
Eli Lilly & Company

With many years of drug hunting experiences in the industry, I found promoting innovative statistical methods/tools is most challenging. Quite often it's not the concepts themselves but how you convey them. Perseverance and patience also help.

Shu-Yen Ho, PhD
GlaxoSmithKline

I would like my friends regard me as a marathon go-er because I keep going and I hate to lose the miles I have already accumulated. Meanwhile I do also want to enjoy life along the way. So far I enjoy my 11 year old daughter and 8 year old son the most. Being able to provide them a decent growth environment and to influence them in the best possible way that I perceive, just makes me feel great.

Greg Wei, PhD
Pfizer, Inc.

"To a statistician, the reason for not to play those slot machines in the casinos is so convincing. Because it is like to prove the large number theory by running a simulation funded by your own hard-earned money. However, regardless the truthfulness of this analogy to statisticians, the real world is following a more optimistic "small number theory", that is you will gain nothing unless you do it, and you may get lucky."

Timothy Chen, PhD
Southwestern Baptist Theological Seminary, Texas

Life is a MCMC. Monte-Carlo is random, not haphazard. Markov chain follows a certain mechanism. Life has both random and deterministic components. But after a lifetime of MCMC, each person can build a tapestry of life with a beautiful distribution.

ChienPai Han, PhD
University of Texas, Arlington, Texas, USA

Pretest leads to better solution in your life

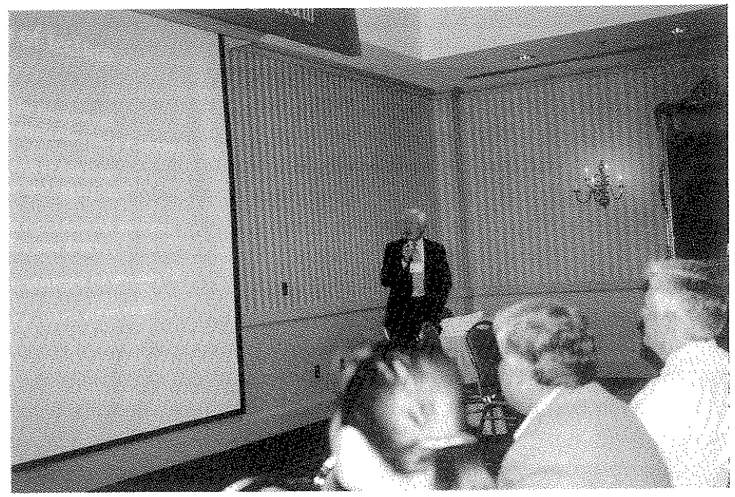
Anges Hsiung, PhD
National Health Research Institute, Taiwan

Life is a positive-drift random walk, filtering out noise and looking for signal.

William Wei, PhD
Temple University, PA, USA

The job of a statistician is to help people see the world through a small window.

Strategies for Managing Risk Associated with New Drugs: A Statistical Perspective on the Issues



Keynote Speaker
Robert T. O'Neill, Ph.D.
Director, Office of Biostatistics, CDER, FDA

The management of risk associated with exposure to new drugs in the marketplace recently has been receiving considerable attention in the medical and lay literature as well as in regulatory discussions. This focus on risk management has occurred, in part, because risk management is viewed as a necessity to address the problem that over the last few years several new drug products have been withdrawn from the market place for safety reasons. The scientific community and the public in general have questioned why. It can be argued that in order to manage risk, one needs to estimate it so that risk can be communicated to patients, prescribers and the public at large. Estimation of risk encompasses statistical quantification of the risk, which involves a variety of statistical methods, concepts, data collection strategies and study designs. Because statisticians have not devoted substantially the same attention to design, analysis and interpretation of safety studies and study outcomes as they have for efficacy studies and outcomes, statisticians involvement in this area of risk assessment can benefit the risk management effort by insuring the use of more statistically appropriate methods and by increasing the level of statistical attention to the problem.

A series of published literature (1, 2, 3) by FDA and by others over concern for whether the removal of products from the market indicated a problem in the evaluation of drug safety has spurred a public discussion and a new visibility of safety assessment. Recent experiences with the removal from the market for

safety reasons of Seldane (terfanadine), Hismanal (astemizole), Posicor (mibefradil), Duract (bromphenac), Propulsid (cisapride), fenfluramine/dexfenfluramine, Lotronex (alosetron) and Rezulin (troglitazone) have motivated these public concerns and responses. As a result, FDA developed a framework for risk management and issued a report titled 'Managing the Risks from Medical Product Use and Creating a Risk Management Framework' (4). This report describes in detail how FDA views the framework for the management of risk in the pre-market and post-market environments, and provides recommendations and options for various strategies that might be used to manage and communicate risk. This framework includes identifying the sources of risk from drug products, namely known side effects which occur that are either avoidable or unavoidable, unanticipated risks, risk from medication errors, and from product quality defects all of which can lead to injury, death. The components of pre-market safety assessment and risk management include the data and information from randomized comparative trials, and from unblinded non-comparative cohorts exposed to the drug from which estimates of incidence and/or relative risks are obtained to weigh benefit vs. risk, especially for the serious events. The communication and management of risk is accomplished, in part, through the public dissemination of the drug's label and its contents. The components of post-market safety assessment and risk management include adverse report screening and evaluation, the submission by drug sponsors to FDA of a periodic safety update report (PSUR), special epidemiological safety studies, and specialized risk management plans for each drug as needed.

The statistical aspects of this problem involve making the right choice of metrics of risk that allow an appropriate statistical characterization and quantification of uncertainty, the recognition of and accounting for bias in risk estimates, and choosing from the variety of statistical approaches to the estimation of risk, relative risk, exposure time dependencies, etc. There are several metrics of risk, each of which may be more appropriate under the circumstance. These include those metrics that are appropriate for single exposure cohorts, such as crude rate, occurrences per unit of time exposure, the life table or cumulative incidence rate, the hazard rate, and competing risks. For comparative cohorts, where the comparison of risk in two or more separate cohorts is the focus, metrics such as hazard ratios, odds ratios, and relative risks are the usual choices.

Despite the availability of these metrics, most safety assessment experience derived from the medical literature suggests a primitive, naïve approach to the problem. The simplistic view of incidence is a single time independent crude rate often used in the medical literature to describe the adverse event rates (2, 5, 6, 7). A more appropriate, yet misunderstood view of incidence, requires the recognition that risk is not constant and that it is a function of several identifiable factors, especially exposure time. (8, 9). Another naïve understanding of incidence involves how most people quantify an incidence rate when no events are observed in a defined cohort. One way to do this when no events have been observed in a cohort of N exposed patients is to place an upper 95% or 99% confidence interval on the unknown rate. In the first instance, the rule of three applies and in the second the rule of seven. This would mean that an upper 99% confidence interval for no events observed in N patients would be approximated by 7/(N+1) (10, 11). Rational risk management requires us to distinguish between these metrics which characterize incidence because we cannot effectively communicate risk, and thus manage it without understanding these distinctions.

For example, the label of a new drug is the primary manner in which information about use of a new drug is promulgated to physicians, patients and health care providers. Among other information, the drug label contains quantitative estimates of risks of certain adverse events, their time dependencies, and in some instances, patient monitoring strategies intended to prevent or minimize the occurrence of a serious adverse event. Take for example, the WARNING section for non-steroidal anti-inflammatory drugs (NSAIDS) which states that 'Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time without warning symptoms, in patients treated chronically with NSAID therapy... these appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.' This is a layman version of stating what the hazard rate is for serious gastrointestinal events (12).

Another simplistic approach that is often used in estimating rates from two or more studies is to combine the numerators and denominators of crude incidence rates from each study into a combined overall incidence rate. Without controlling for time, this approach will always underestimate the true risk. Ignoring the control for time, especially when a life table approach is applicable but ignored in favor of a crude binomial type rate, is to underestimate the width of the confidence intervals for cumulative rates, again understating the uncertainty of the estimates.

In order to fully characterize the multiplicity of adverse events and patterns of events and exposures that may be observed in a single patient in a clinical trial and subsequently to estimate event rates, relationships, and risk factors that are associated with these events, it is necessary to take a more global approach to the data contained in a patient's case record. Most medical officers, when evaluating the safety profile of a new drug, are interested in the longitudinal, chronological profile of a patient in a clinical trial. This allows one to judge the time progression of lab values from pre-treatment status to on treatment status, the censoring patterns, the multiple events of different types that may occur to an individual subject, and may even be recurring. Visual graphics, plots and related pictures of intermittent, chronological information are very useful here. For time to event data for which patients have different covariate levels related to differential event rates, there has been recent work on how to present this information so that it can be better interpreted (13). Dubin, Muller and Wang have suggested event history graphs of censored survival data. The analysis of such data from a population perspective, can be viewed as a type of event history analysis (14) in which time dependent confounders, and structural failure time models may help characterize and estimate risks that are functions of time and risk factors. Keiding (14) has proposed such approaches for observational data, which is often the form that safety data takes when single exposure cohorts are evaluated for risk assessment.

When drugs are approved and made available to patients, this phase is typically called post-market surveillance, and has a particular focus on safety evaluation. This phase of surveillance is when new drugs are in general use in large diverse populations and adverse events that are rare or that are associated with concomitant use of other drugs often are observed and reported to FDA. In this situation, the challenge is to assess whether such patterns of occurrence are real, represent causal associations, and whether any regulatory actions, like updating the label, restricting use, or market withdrawal, should be taken. The MedWatch form is the vehicle that is used to collect and report such patient level adverse events to FDA and to manufacturers. These reports can be summarized as counts and

are amenable to exploratory statistical analyses that can help signal associations worthy of more in depth evaluation or follow-up work. FDA has been exploring and developing various approaches to evaluating such data bases, which now are very large, including over two million reports and many drug—adverse event combinations. If one views the counts of all drug—adverse event combinations as a large sparse two by two table, it is possible under assumptions of independence of drugs and events to calculate expected counts, compare them to observed counts, and model the ratios of these observed to expected counts for the purposes of identifying those combinations that appear much larger than expected. This concept is behind the Bayesian data mining item association methods that DuMouchel developed for FDA to address signals of unusually high associations between drugs and adverse events (15, 16, 17). This problem becomes very complex when multiple drugs or multiple related adverse events are responsible for the higher than expected observed counts.

In some situations, only a large clinical trial whose objective is to evaluate a specific aspect of safety of a new drug will provide answers. Recently, large randomized controlled clinical trials designed and powered for safety outcomes have been conducted (18, 19). These studies present new challenges as new statistical issues are being identified for such safety focused studies. Multiple endpoints, informative treatment related censoring, time dependent surrogate markers indicative of later serious events and multiple risk factor identification are just some of the statistical issues that arise in these studies. Statisticians must contribute more to the design, analysis and interpretation of these studies in the future. When randomized studies cannot be conducted, observational epidemiological studies can be. A recent large case-control study examining the relationship between phenylpropanolamine and the risk of hemorrhagic stroke in women was conducted, published and served as the basis of a regulatory action to withdraw this drug from some uses (20). This study was an interesting example of group sequential designs being applied to a case control study.

Risk assessment, communication and management is likely to be the theme for the next decade as we deal with the management of benefit and risk for the introduction of new drugs in the marketplace. Statisticians have played a critical role in the planning, analysis and interpretation of efficacy studies, but have been much less involved in safety studies. As a result, the sophistication of safety studies and quantitative safety assessment is substantially less rigorous and developed. It is time for statisticians to contribute more to quantitative risk assessment for new drugs and to bridge the disciplines of epidemiology, clinical pharmacology and clinical trialists. Most clinical trials can also be evaluated in more depth for safety signals such as biomarkers of serious events that are observed or cause withdrawal from trials. The challenges here are exciting but must be met if we are to contribute to the future management of risk associated with exposure to pharmaceuticals.

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Emerging (and Continuing) Issues for Statisticians in Drug Development from the Perspective of an Industry Statistician

Keynote Speaker
George W. Williams
Bristol-Myers Squibb Company

The pharmaceutical industry anticipates an increasing volume of leads through technological advances in drug discovery. Clinical trials are becoming more complex in terms of the study of more complex diseases, more demanding customer information needs, and increasing number of subjects per trial. The life span of novelty of new drugs is becoming shorter. Consequently, the pharmaceutical industry is increasingly giving attention to improving the drug development process. I would suggest that in all of these changes, there is an increasingly important and expanding role of the discipline of statistics.

Pharmacogenomics and pharmacogenetics are starting to have an impact on drug discovery and drug development.

Pharmacogenomics is the study of the relationships between genetic variability and drug response. Single nucleotide polymorphisms, or SNPs, are the most common form of DNA sequence variability. Associations of SNPs and other genetic variants with disease, drug response, and adverse events have been documented in the scientific literature. As noted by Roses (2001), if trials are limited to those patients with a drug-responsive SNP defined in earlier studies, then clinical trials could be performed faster, with fewer patients and less expense. This would, of course, segment the patient group for which the drug is indicated. In the areas of pharmacogenomics and pharmacogenetics, ethical and data privacy issues are fundamental.

A new technology in drug discovery allows the measurement of gene expression on a wide scale, namely microarrays. As Holder et al (2001) note, the large number of genes, multiple levels of variation, and typically small number of experimental units combine to make analysis of data from these arrays challenging. There is inherent noise associated with the assay process. Basic questions from microarray experiments include: For which genes have we detected expression? For which genes has the expression level changed between experimental conditions? As Simon et al (2002a, 2002b) note, the design and analysis of microarray experiments should be tailored to study objectives or questions. For predetermined class comparison, the objective is to establish whether gene expression profiles differ and identify genes responsible for differences. For class discovery, the objective is to discover clusters among specimens or among genes. For class prediction, the objective is to predict phenotype using information from gene expression profiles.

Contributions to these emerging areas of early phase drug discovery and development from the field of statistics include attention to such classical statistical issues as data quality, experimental design, data visualization, and analysis. In microarray experiments, as in experimentation in general, a well planned design is more likely to lead to interpretable results, and appropriate designs are dictated by particular study objectives. In terms of a specific design issue, replication is critical and yet it is recognized that the ability to replicate will be limited due to limited supply of samples, time, and resources. As one would expect with these types of experiments several traditional analysis issues exist. For example, missing values arise. As noted by Trobyanskaya et al (2001), missing values occur for diverse reasons, including simply due to dust or scratches on the slide. There is not a large published literature concerning missing value estimation for microarray data, but much work has been devoted to similar problems in other fields, and these methods are now being applied to microarray data. In the case of high density arrays, for some study objectives a very large number of statistical tests will be carried out on the data. Carrying out such a large number of tests will result in an elevated false positive rate if a correction to nominal p values is not applied. To summarize these comments regarding microarrays, Holder et al (2001) note although microarrays hold great promise for helping researchers understand complex patterns of gene expression, in some ways they are not different from other assays and classical statistical issues arise.

As we move from drug discovery to clinical trials, we should at least provide one example of the contribution of statistics to drug formulation. One of the challenges of developing a formulation and process for a new chemical entity is determining whether the proposed formulation or process will be sufficiently robust for scaling from the laboratory to the factory. A standard experimental approach whereby one factor is varied and all others remain constant, will give some level of understanding of the system, but does not provide any insight into the impact of other possible variables in the system. Sophisticated experimental designs allow multiple independent variables to be studied with a limited number of batches.

Researchers and patients wish to assess the effectiveness of promising new treatments as quickly as possible. Surrogate endpoints constitute an effort to address this issue and have

received considerable attention in the medical statistical literature. The extent to which a biomarker is appropriate for use as a surrogate endpoint in evaluating a new treatment depends on the degree to which the biomarker can reliably predict the clinical benefit of that therapy as compared to a standard therapy. As pointed out by Fleming and DeMets (1996), the treatment may affect the disease process through multiple pathways. Such considerations underlie the difficulty of statistical validation of a response variable as a surrogate endpoint. While it is difficult to determine whether a laboratory measurement or physical sign can be a useful substitute for the target clinical outcome, it is still desirable to quantify the proportion of treatment effect explained by a surrogate relative to the overall net treatment effect. As Buyse et al (2000) noted, although others have expressed reservations about the validation of surrogate endpoints, in practice, the need to evaluate treatment effects as fast as possible will remain important.

Let us now turn to another area of clinical trial design, equivalence or non-inferiority trials. As Quan, Bolognese, and Yuan (2001) noted, as medical science advances, some of the focus in new drug development has been shifted to develop new medicines which may not necessarily be more effective compared to currently marketed drugs, but have some other advantages, like reducing toxicity, improving patients' comfort, or enhancing patients' convenience. As there is increased need for comparative data, active controlled clinical trials are frequently employed in equivalence or non-inferiority designs. Design and analysis issues (choice of delta, analysis set, assay sensitivity, choice of control group, quality of trial conduct) need to be carefully considered. A critical issue in the design of such trials is the definition of the margin of equivalence or "delta."

As noted by Gould (2001), interim findings of a clinical trial often would be useful for adjusting the sample size if necessary to provide the required power. Strategies for carrying out the interim examination that have been described over the past several years include internal pilot studies and blinded interim sample size adjustment. Clearly, methods not requiring unblinding the data before completion of the trial would be most appropriate. Moreover, extending a trial has its risks. The investigators/patients enrolled later in the course of a trial are not necessarily the same as those recruited /entered early.

As noted by Berry (2001), designs of phase II and III clinical trials are usually static in that the sample size and any prescription for assigning treatment, including randomization protocols are fixed in advance. Results observed during the trial are not used to guide its course. There are some exceptions. For example, some Phase II cancer trials have two stages with stopping after the first stage possible if the results are not sufficiently promising (Simon, 1989). Berry (2001) describes a family of designs that are dynamic in the sense that observations made during the trial can affect the subsequent course of the trial. Concern noted by Chi, Hung, and O'Neill (2001) are not so much the technical limitations to methodology for adaptive flexible designs as to the practical aspects of operational implementation of them so as not to introduce bias.

Analysis issues in clinical trials which will continue to require attention by statisticians include the analysis of missing data and multiplicity issues. It is interesting that we noted similar key analysis issues in drug discovery as

well. Missing response data is a very common occurrence for longitudinal studies because of treatment drop out, mistimed measurements, subjects being too sick to come to the clinic to be measured, and so forth. Often, missing response data in these studies is non-ignorable in the sense that the reason for missingness often depends on the missing values themselves. As summarized by Ibrahim, Chen, and Lipsitz (2001), there is an extensive literature of methods for maximum likelihood estimation with nonignorable missing data using selection models, pattern mixture models, and conditional linear models. Last observation carried forward (LOCF) approaches are common in the analysis of pharmaceutical clinical trials. Another issue in the analysis of clinical trials requiring continuing attention is the area of multiplicity. Multiplicity can arise in many different ways including multiple treatment groups, multiple outcome variables, multiple subgroups, and interim analyses. Approaches to the handling of these issues are critical to prespecify in the protocol or data analysis plan before unblinding of the trial. Closed testing procedures and hierarchial procedures are some examples of approaches that are currently successfully applied.

Traditionally, much attention has been given to statistical methods for the analysis of efficacy data in clinical trials with somewhat less attention applied to safety data. Recently, specific attention is being given to the challenging issues involved in the analysis of safety data within the context of clinical trials as well as spontaneous reports of adverse drug reactions. The FDA has been investigating methods for the analysis of data collected through the spontaneous adverse experience reporting system. Specifically, data mining algorithms (e.g., DuMouchel's empirical Bayesian data mining approach) in conjunction with visual graphic displays are being considered. (DuMouchel, 1999; O'Neill and Szarfman, 2001) Turning to clinical trial data, Gould (2001) notes that analysis of safety/tolerability differ fundamentally from analyses of efficacy. Tests for treatment differences in adverse event risk that had not been identified in the design of the trial present potentially serious multiplicity and interpretation issues because the outcomes generate the hypotheses. Information about safety including clinical signs and symptoms, vital signs, etc. can be expressed in a natural triage. A relatively small number of safety issues (e.g., specific adverse events or collections of them) ordinarily will be identified a priori as important and hypotheses about them can be tested like efficacy. All other events are handed primarily descriptively with the particular approach depending on their frequency. As Chuang-Stein, Le, and Chen (2001) note, there are many other areas in which statisticians can assist in efforts to understand the safety profile of a pharmaceutical product. Statisticians can further develop methods for risk assessment that will facilitate benefit/risk assessment.

There is increasing interest in quality of life and other outcome data assessing patient's well being. As noted by Martin (2001), patient reported outcomes (PROs) include quality of life, functioning, symptoms, etc. Issues include the many different measures and scales both generic and disease specific, the subjective nature of such measures, and the lack of a gold standard in many cases. Scales and measures need to be validated. Statistical challenges include the multiplicity issues that arise in such a multi-dimensional context as quality of life and patient reported outcomes.

Pharmaceutical companies increasingly need

to demonstrate cost-effectiveness of its products in addition to simple effectiveness. Payers, formularies, reimbursement decision bodies, etc. are requiring health economic information. For example, in the UK, the National Institute of Clinical Excellence (NICE) has been established to address cost as well as effectiveness for treatments for the National Health Service.

Moving beyond the individual clinical trial, meta-analysis has been an important component of evidence-based medicine. Meta-analysis, or quantitative overviews, have now been applied to many areas of medicine. Meta-analysis generally results in a number representing an average treatment effect, and this has sometimes led to controversy over whether the clinical trials were similar enough with regard to treatments, populations, quality of conduct, etc. for meaningful combination.

Let us now turn our attention to other approaches for extracting information from existing data. Given the wide use of advanced data base technology and the efficient storage of huge amounts of data, there has been considerable interest in data mining approaches or Knowledge Discovery in Databases (KDD) methods. Data mining methods and algorithms include recursive partitioning (e.g., CART) and other computer intensive methods. However, it is critical that fundamental attention be given to the data quality of such data that is being analyzed, and, consequently, considerable energy can be expected to be devoted to data preparation. The validity of models that are derived need to be fully tested with independent samples (e.g., the concept of training and test sets). The models need to be evaluated by domain experts (e.g., physicians) to ensure that they make sense, and, hence, conclusions are interpretable. Results of data mining activities frequently are hypothesis generating (Shnaider and Schneider, 2001).

Policy matters related to the pharmaceutical industry and statistical issues have received considerable attention recently in various forums. Specifically, the role of data safety monitoring boards has received particular attention (FDA, 2001). As Ellenberg (2001) noted, in recent years, regulators have encouraged sponsors to establish independent DMCs to monitor trials with endpoints such as mortality or other major events such as well defined progression of a fatal or disabling disease. However, issues have arisen regarding the requirements for an independent DMC. It may be the case that individuals within a company who have been involved with the development of the product being tested have great insight into the product's properties that could be useful to monitoring the trial. It may be efficient to have the data processed and analyzed by the statistical/data management group at the company. Hence, one or more individuals from that group will of necessity have access to the interim data in order to prepare and present the interim analysis to the DMC.

A second policy issue to consider is relative to the reporting of clinical trials. Journal editors and others have given attention to issues involved in the reporting of clinical trials and data access. As Altman et al (2001) note, there is evidence that the quality of reporting of randomized, controlled trials is less than optimal. The CONSORT standards provide a particularly helpful guideline in this regard and the application of those standards and their revisions should be encouraged. Readers should not have to speculate as to the methods used. This information should be transparent so that readers can differentiate trials with unbiased results from those with questionable results. It was noted at a recent FDA (2001) conference as well as in a policy report in the New England Journal of Medicine (Bodenheimer, 2000) that there is concern about the prompt reporting of clinical trials even negative trials.

The need for statistical excellence in drug development will not decrease. The technical skills of the statistician are required, but additionally the logical thought and attention to precision and accuracy that the statistician has are also required. Excellent communication skills are critical to the success of the statistician (Pocock, 1995). As statistical software has become increasingly available, statisticians must adapt. Given the availability of software, statisticians now are able to teach scientists and other researchers how to conduct their own routine analyses. Statisticians are freed up to conduct the more complicated or unusual analyses. Additionally, the statistician must become more efficient providing timely information. As Waife (2001) notes, there is an assumption that all of the changes we have been discussing in the pharmaceutical industry will not be accompanied by increased levels of human resources. Hence, there will be pressure on organizations to respond with effective time and resource savings.

The training of statisticians should increasingly emphasize areas of biological research (e.g. genetics, molecular biology, and computational biology). Successful solutions in medicine will require cross-disciplinary teams to arrive at those solutions. As Tobi et al (2001) noted, research is increasingly collaborative. The biostatistician must be an integral member of the team and have a substantial involvement at early stages in the planning and design of studies. In order to contribute in such a fashion, the biostatistician must have more than a summary knowledge of the subject matter. Appropriate knowledge of the relevant epidemiology is important. However, methodological skill and research is fundamental for the statistician. The statistician must keep up with biostatistical as well as major medical literature in order to familiarize him/herself with new techniques and ideas.

To summarize, in this review of emerging issues for statisticians in drug development, we have superficially covered many areas from drug discovery to drug development, from design to analysis, some aspects of policy, and finally the role and training of statisticians. As DeGruttola et al (2001) stated, research in biostatistics and technology is yielding promising new ways of understanding and measuring human disease processes. Genome sequencing, DNA microarrays, proteomics, and magnetic resonance imaging are giving rise to new tools of biostatistics and epidemiology that are being utilized and are producing more information than was obtained through previous methods.

It is important to note that I have commented on the need to recall basic principles of experimental design, variability, replication, testing of adequacy of models, etc. Although new technologies are becoming available to aid in drug discovery and development, we must remember to continue to value the core principles of statistical science that have been established over the last sixty years or so. As Simon (1991) noted a decade ago, "(We) will see many exciting medical developments but the need for statistical excellence in drug development and treatment evaluation will not decrease." It is interesting to note that one of the top eleven medical developments of the past millennium was the application of statistics to medicine

(NEJM, 2000). I would suggest that statistical considerations are now even more vital in clinical development than in the past.

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O'Neill, R. T. and Szarfman, A. (2001) Some U.S. Food and Drug administration perspectives on data mining for pediatric safety assessment. Current Therapeutic Research 62: 650-663.

Pocock, S.J. (1995) Life as an academic medical statistician and how to survive it. Statistics in Medicine 14: 209-222.

Quan, H., Bolognese, J., and Yuan, W. (2001) Assessment of equivalence on multiple endpoints. Statistics in Medicine 20: 3159-3174.

Roses, A. D. (2001) Pharmacogenetics. Human Molecular Genetics 10: 2261-2267.

Shnaider, E. and Schneider, M. (2001) Soft regression: a data mining tool. Data Mining and Computational Intelligence 68: 251-272.

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Simon, R., Radmacher, M.D., and Dobbin, K. (2002b) Design of studies using DNA microarrays. Biometric Research Branch. National Cancer Institute.

Tobi, H., Kuik, D.J., Bezemer, P.D., and Ket, P. (2001) Towards a curriculum for the consultant biostatistician: identification of central disciplines. Statistics in Medicine 20: 3921-3929.

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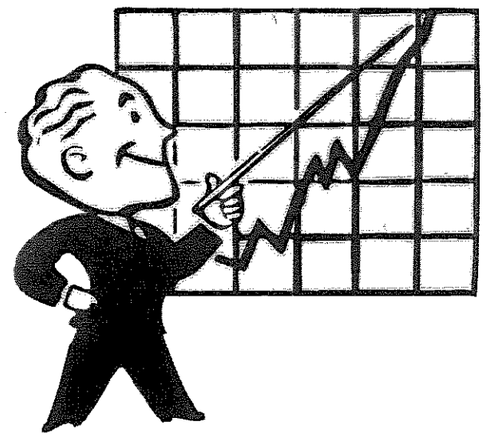

Brief Biography of Candidates

CANDIDATES FOR PRESIDENT-ELECT

SHEN, C. Frank

[PRESENT POSITION] Director, Clinical Discovery Biostatistics and Data Management, Bristol-Myers Squibb Co. **[FORMER POSITIONS]** Director and Associate Director, Non-clinical Biostatistics, Bristol-Myers Squibb Co., 1996-2001; Manager and Biometrician, Biometrics Research, Merck & Co, 1993-1996; Research Statistician/ Sr.Statistician/Statistician, Biometrics, Wyeth-Ayerst Research, 1989-1993. **[DEGREES]** Ph.D., 1992, Statistics, Temple U.; M.S., 1987, Statistics, Temple U.; M.E.S., 1985, Chemical Engineering, Lamar U.; B.E., 1978, Chemical Engineering, Chung-Yuan U., Taiwan. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Statistical collaboration or leadership in the following areas: computational chemistry and computational biology in Drug Discovery; natural product taxonomy; microbial medium optimization; psychopharmacology; pharmacokinetics; data warehousing and mining; pharmacodynamics; bioequivalence; clinical pharmacology; pharmacogenomics; catalyzing scientific research with statistical thinking. **[PUBLICATIONS]** "Testing Non-additivity of Biological Activity in Combinatorial Chemistry," 2001, to be appeared at Combinatorial Chemistry & High Throughput Screening; "Binary Formal Inference-Based Recursive Modeling Using Multiple Atom and Physicochemical Property Class Pair and Torsion Descriptors as Decision Criteria," 2000, J. Chem. Inf. Comput. Sci; "Experimental Autoimmune Encephalomyelitis is Exacerbated in Mice Lacking the NOS2 Gene," 1998, J. of Immunology; "Robust and Bootstrap Testing Procedures for Bioequivalence," 1994, J. of Biopharmaceutical Statistics; plus 15 other authored or co-authored manuscripts in J. of Medicinal Chemistry, Arthritis and Rheumatism, SUGI Proceedings, Psychopharmacology, Pharmacology & Biochemistry & Behavior; Drug Development Research; Annuals of the NY Academy of Sciences; Fundamental and Applied Toxicology. **[ICSA ACTIVITIES AND OFFICES HELD]** Board of Directors (2000-2002); Chair of Constitution Committee (2001); Member of Nomination and Election Committee (2001), Long Range Financial Planning Committee (2000) and Applied Statistical Symposium Committee (2002, 2000, 1997). **[RELATED PROFESSIONAL ACTIVITIES]** Associate Editor, J. of Biopharmaceutical Statistics (2002-2004); PhRMA Biostatistics & Data Management Steering Committee member (2000-2003); Vice Chair, District 1, ASA Council of Chapters (2000-2002); ASA Committee on Career Development (2001-2003); Workshop chair (1999) and co-chair (1998) of the Midwest Biopharmaceutical Statistics Workshop; Symposium Chair (1995-1997) of the ASA/NJ Chapter; Program Chair (1996-1997) of the ASA Princeton-Trenton Chapter; Co-chair (1997) of the ASA/SPES Spring Research Conference; International Biometrics ENAR regional advisory board member (1997-1999).

[STATEMENT] I am truly honored to be considered as a candidate for the President of the ICSA, and I thank the Nominating Committee for this opportunity. International Chinese Statistical Association is a vibrant organization that has grown so much with our growing profession, and I am proud to be part of its growth. Our members have become major statistical work force among industry, academia, and government in this country as well as around the world. They also hold important offices and actively participate in other statistical societies such as ASA, ENAR/WNAR and IMS. Our Journal, Statistical Sinica, is one of the most cited statistical journal in the world. The superior program in our annual Statistical Symposium has drawn high attendance with extended duration from one day ten years ago to two and half days this year. While we can celebrate these successes, there are still challenges and issues for the ICSA to address over the next several years. We need to be more effectively in connecting and serving our members. It is our essential mission to provide our members opportunities to enhancing their technical as well as leadership skills. Our web site needs to be enhanced to better communicate information globally such as career opportunities and "e-mentors" to provide career advice. We need to increase the diversity of our membership and continue to maintain our close linkage with other statistical societies. Our Board needs to build better mutual trust so the joint efforts exceed the sum of our individual wisdom. We need to be more focused on strategic planning in order to devise a plan that will guide us for the next five to ten years. Last but not the least; we need to nurture our own leaders in our organization.

When I attended the first ICSA Applied Statistical Symposium held in NIH in 1990, I was still a graduate student who just entered the industry and all I wanted was to be a member. When I started to get involved in organizing Applied Statistics Symposium year after year, all I wanted was to make every symposium a success and I felt so rewarding when I saw my friends and new members enjoy the conference. When I started to serve on the Board, I decided to do the best I can to sustain the quality and success that so many forerunners had contributed to. Presidency of the ICSA would be an enormous challenge. Having served in multiple committees and Board of Directors of ICSA for the last five years, I think I am up to the challenge. I shall like to attempt it.

SUN, Don X.

[PRESENT POSITION] Member of Technical Staff in the Statistics Research Department at Bell Laboratories, Lucent Technologies since 1995. **[FORMER POSITIONS]** Assistant Professor in the Department of Applied Mathematics and Statistics at the State University of New York, Stony Brook, during 1993-1995. **[DEGREES]** B.S. in Applied Mathematics and M.S. in Statistics from Southeast University, China in 1989, Ph.D. in Statistics from the University of Waterloo, Canada in 1993. **[FIELD OF MAJOR STATISTICAL ACTIVITIES]** Dr. Sun's main research interests include statistical design of experiments, quality engineering, signal processing and speech recognition, graphical methods and distributed computing for analyzing massive datasets, data mining, and, in the recent few years, Internet traffic research in measurement, analysis, modeling, and network simulation (http://cm.bell-labs.com/stat/InternetTraffic) **[SELECTED PUBLICATIONS]** He has published over 30 papers in statistics journals including Technometrics, Journal of Quality Technology, JRSS, JASA and engineering journals including Signal Processing, IEEE Transactions on Speech and Audio Processing, and ACM Sigmetrics. Some representative articles are: "A catalogue of two-level and three-level fractional factorial designs with small runs", 1993, International Statistical Review; "Optimal Blocking Schemes for 2^n and 2^(n-p) Designs", 1997, Technometrics (Winner of 1998 Jack Youden prize); "Analysis of Interval Censored Data from Fractionated Experiments Using Covariance Adjustments", 2000, Technometrics (Winner of 2000 Frank Wilcoxon prize); "On the Nonstationarity of Internet Traffic", ACM SIGMETRICS, 2001. **[ICSA ACTIVITIES AND OFFICES HELD]** Dr. Sun is currently a member of the ICSA Board of Directors (2001-2003), and a member of the ICSA communications committee responsible for the ICSA web site since 1997. He developed the first ICSA applied symposium web site in 1997, and since have developed and maintained web sites for most of the ICSA applied symposia and ICSA Conferences. **[RELATED PROFESSIONAL ACTIVITIES]** He is a member of ASA, ASQ, ICSA, and IEEE.

[STATEMENT] The fast growing information technology has generated unprecedented demands for statistics in this Internet age. It creates exciting opportunities for statisticians and the statistics discipline and profession worldwide. A major role of ICSA is to help members to take advantage of the opportunities and to build visibility for statisticians (especially Chinese statisticians) in science and technology beyond our own discipline and profession. I strongly believe that communication/ networking among ICSA members and with members from other professions is the key in achieving this goal. I will focus on some specifics in promoting activities and creating services that meet member's growing needs:

I would like to promote activities in career development for members, especially for the junior members who are at the beginning of their statistics career. As continuing education and learning is one of the most effective way to make advancement in one's career path, it will be very beneficial to members for ICSA to have specialized training programs in the form of short courses, workshops, and tutorial sessions. ICSA has been very successful in providing short courses at the annual Applied Statistics Symposia, so I think we could extend this success to more ICSA sponsored satellite events of short courses and workshops at smaller scales and in different local geographical areas. This effort will not only help members in gaining new knowledge and skills, but also provide more opportunities for building a stronger network among members.

The current ICSA web site has served well for the major association events such as the conferences, announcements, and job postings. But it can do more, especially in strengthening the communication and networking among ICSA members. One approach is to use online news discussion forum for ICSA members to share tips, help each other, and to search for solutions to problems in archives that other members have discussed before. I strongly support the ideas proposed by our Executive Director in expanding ICSA's online services for members. Finally, I sincerely thank all of you for giving me the opportunity to make contribution to ICSA and the continuing support for the ICSA activities.

Brief Biography of Candidates

CANDIDATES FOR BOARD OF DIRECTOR

LI, Hung-Ir

[PRESENT POSITION] Research Scientist, Eli Lilly and Company, 1998-present **[FORMER POSITIONS]** Senior Biostatistics Scientist, Pharmacia and Upjohn, 1991-1998 **[DEGREES]** Ph.D. in Statistics, 1991 **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Non-parametrics, Modelling and simulation, Clinical Statistics

[PUBLICATIONS] "Converting a SAS Data Set to a Flat File: A SAS/AF Software Application", HI Li and PY Lai, 1989, Best contributed paper. SUGI 14 Proceeding, Information Section; "Effect of Dose Escalation Pace on Benzodiazepine Clinical Response", 1995 DIA Annual meeting, Orlando, Florida; "Analyzing panic Attacks as Counts of Discrete Events", 1997, ASA JMS Proceedings, the Biophamaceutical Section; "Effect of Dose Escalation Pace on Benzodiazepine Clinical Response", HI Li, PL Rupple, and AQ Denahan, 1997 , Volume 31, 3, 671-7, Drug Information Journal; "Effect of Heparin-Surface-Modified Intra-ocular Lenses on Postoperative Inflammatory Response in Routine, Glaucoma, and Diabetes Patients" SD Trocme and HI Li, 1998 ASCRS meeting, San Diego, California; "The Clinical Trial Simulation- a Clinical Statistician's Perspectives", Invited speaker, 1999 ASA JSM, Baltimore, Maryland; "Effect of Heparin-Surface-Modified Intra-ocular Lenses on Postoperative Inflammation After Phacoemulsification: A Randomized Trial in a US patient Population", Stefan D. Trocme and Hung-Ir Li, 2000, Ophthalmology, 107:1031-1037 ; "The Usage of Modeling and Trial Simulation in the Early Drug Development", Invited speaker and panelist, 2000 Midwest Biostatistics Workshop, Muncie, Indiana; "Drug-Effect-Concentration and Clinical Trial Simulation" Invited speaker, FDA , Rockville, DC, 2001; "Exploring the Sensitivity of Simulation Results to Underlying Assumptions and Uncertainty: Impact on Clinical Trial Design", Invited Speaker and Panelist, 2nd Clinical Trial Simulation in Drug Development Conference, Washington, DC, 2001; "In Silico Simulation Beyond Computational Chemistry Towards The Future Of Computational Biology and Clinical Development ", Sean Ekins and Hung-Ir Li, Lilly white paper, 2001 **[ICSA ACTIVITIES AND OFFICES HELD]** ICSA Bulletin Editorial Board, 2001; Program Committee, 2001 Applied Statistics Symposium **[RELATED PROFESSIONAL ACTIVITIES]** Referee to Communications in Statistics, 1992, 1998; American Statistician, 1993; Journal of Biopharmaceutical Statistics, 1993, 1996, 1997; Chapter Representative , American Statistical Association Southwest Michigan Chapter, 1995-1997; Session Organizer and Session Chair, JSM, ASA, 1999; Session Organizer and Session Chair, 6th Great Lake Symposium on Applied Statistics, 2000; Session Organizer and Session Chairs, ISCA Applied Statistics Symposium, 2001

WEI, Greg Cheng Gang

[PRESENT POSITION] Associate Director, Biometrics, Pfizer-Groton. **[FORMER POSITIONS]** Principal Statistician, Sanofi-Winthrop. **[DEGREES]** Ph.D. 1989 University of Wisconsin-Madison. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Censored Data Analysis Using Data Argumentation, Optimal Design for Estimation of PK Parameters, Release Target Determination, Sample Size Estimation for Bioequivalence Studies, Population and Individual Bioequivalence, Applications Mixed Effect Modeling in Clinical Trial Data. [PUBLICATIONS] Greg C.G. Wei and Martin A. Tanner, "Posterior Computation for Censored Regression Data",JASA, Sept. 1990, Vol 85. Greg C.G. Wei and Martin A. Tanner, "A Monte Carlo Implementation of the EM Algorithm and the Poor Man's Data Augmentation Algorithm", JASA, Sept. 1990, Vol 85. Greg C.G. Wei and Martin A. Tanner, "Calculating the Content and Boundary of the Highest Posterior Region via Data Augmentation", Biometrika 1990, Vol 77. Greg C.G. Wei and Martin A. Tanner, "Application of Multiple Imputation to the Analysis of Censored Regression Data",Biometrics 47, Dec. 1991. Dale Yu, Sam Hutcheson, Greg Wei, Vijay O. Bhargava, and Scott Weir, "A Comparison of Population and Standard Two-Stage Pharmacokineti Analysis of Vigabatrin Data", Biopharmaceutica & Drug Disposition, Vol. 15, 1994 Greg C.G. Wei, "Applications of the Linear Mixed Effects Models in Statistical Analysis of Assay Validation", Journal of The Chinese Statistical Association, Vol. 33, No. 2., 1995 Alexander W. Boddy, Fred C. Snikeris, Robert O. Kringle, Greg C.G. Wei, James A. Oppermann, and K. K. Midha, "An approach for Widening the Bioequivalence Acceptance Limits in the Case of Highly Variable Drugs", Pharmaceutical Research. Vol. 12, No.12, 1995 Greg C.G. Wei,"Experimental Design for Estimating Area Under Curve by the Trapezoidal Approximation in Destructive Sampling", Drug Information Journal, Vol 31, No. 4, 1997. Greg C.G. Wei,"Determination of Release Limits for Drug Products", Journal of Pharmaceutical Statistics, Vol. 1, No.1, 1998. G.A. Maier, G.F. Lockwood, J.A. Oppermann, G. Wei, P. Bauer, J. Fedler-Kelley and T. Grasela, " Characterization of the Highly Variable Bioavailability of Tiludronate in Normal Volunteers Using Population Pharmacokinetic Methodologies",European Journal of Drug Metabolism and Pharmacokinetics, 1999 Vol. 24, No. 2. George Foulds, Lucia Laboy-Goral, Greg C.G. Wei, and Glen Apseloff, "The Effect of Azithromycin on the Pharmacokinetics of Indinavir", Journal of Clinical Pharmacology, 1999; 39:842-846. J. Quiroz, N. Ting, G.C. G. Wei, and R. Burdick, "A Modified Large Sample Approach in the Assessment of Population Bioequivalence", Journal of Biopharmaceutical Statistics, Vol. 10, No. 4, 2000. J. Quiroz, N. Ting, G.C.G. Wei, R. Burdick "Alternative Confidence Intervals for the Assessment of Bioequivalence in Four-period Crossover Designs". (will appear on "Statistics in Medicine") **[ICSA ACTIVITIES AND OFFICES HELD]** ICSA member since 1989. Member of The Organizing Committee for ICSA Applied Statistics Symposium of 1998. **[RELATED PROFESSIONAL ACTIVITIES]** member of DIA

CHEN, Jiahua

[PRESENT POSITION] Professor of Statistics
Department of Statistics and Actuarial Science University of Waterloo, Waterloo, Ontario, N2L 3G1 Canada **[FORMER POSITIONS]** Associate Professor, Assistant Professor, Department of Statistics and Actuarial Science, University of Waterloo. Visiting Scientist, Mount Sinai Hospital. Postdoctoral Fellow, Bowling Green State University. **[DEGREES]** Ph.D. 1990, University of Wisconsin-Madison. Major: Statistics; minor: Computer Science and Mathematics. M.S. 1985, Institute of Systems Science, Academia Sinica, China. Major: Statistics. B.S. 1982, University of Science and Technology of China. Major: Mathematics. **[PRIMARY RESEARCH INTERESTS]** Statistical Inference: Finite mixture models; empirical likelihood methods; asymptotic theory. Experimental Designs: Fractional factorial designs, supersaturated designs. Genetic Statistics: Linkage analysis. Survey Sampling: Nearest neighbor imputation, hot-deck imputation. Applications: Statistical problems in Fisheries. **[SELECTED PUBLICATIONS]** Dr. Chen published over 60 papers in a variety of refereed journals. Most recently published articles include: Chen, J. and Wu, C. (2001). Estimation of distribution function and quantiles using the model-calibrated pseudo empirical likelihood method. Tentatively accepted by Statistica Sinica. Chen, H., Chen, J. and Kalbfleisch, J.D. (2001). A modified likelihood ratio test for homogeneity in finite mixture models. Journal of Royal Statistical Society, B 19-29. Wei, L. and Chen, J. (2001). Empirical bayes estimation and its superiority for two-way classification model. To appear in Probability and Statistics Letters. Chen, J., Sitter, R.R., and Wu, C. (2001). Using Empirical Likelihood Methods to Obtain Range Restricted Weights In Regression Estimators For Surveys. To appear in Biometrika. Chen, J. and Shao, J. (2001). Variance estimation under nearest neighbor imputation. J. Amer. Statist. Assoc. 96 260-269. Chen, J., Kalbfleisch J.D. and Romero Hidalgo, S. (2001). Genetic data analysis of affected sib pairs: Case study. To appear in Canadian Journal of Statistics. Chen, H. and Chen, J. (2001). Large sample distribution of the likelihood ratio test for normal mixtures. Probability and Statistics Letters. 52, 125-133. Susko, E., Chen, J. and Kalbfleisch, J.D. (2001). A Diagnostic Tool for Mixture Models. Journal of Statistical Computation and Simulation. 69, 293—314. Cadigan, N. and Chen, J. (2001). Properties of robust M-estimators for Poisson and binomial data. Journal of statistical computation and simulation. 70, 273—288. Chen, H. and Chen, J. (2001). The likelihood ratio test for homogeneity in the finite mixture models. Canadian Journal of Statistics. 29, 201-216. Chen, J. and Cheng, P. (2000). The limiting distribution of the restricted likelihood ratio statistic for finite mixture models. Chinese Journal of Applied Probability and Statistics. 16, 159-167. Zhong, B., Chen, J. and Rao, J.N.K. (2000). Empirical likelihood inference in the presence of measurement error. Canadian Journal of Statistics. 28, 841-852. Chen, J., Rao, J.N.K. and Sitter, R.R. (2000). Efficient random imputation for missing data in complex surveys. Statistica Sinica. 10, 1153-1169. Chen, H., and Chen, J. (2000). Discussion on ''Hybrid resampling methods for confidence intervals" by Chung and Lai. Statistica Sinica, 10, 40-43. Chen, H., and Chen, J. (2000). Bahadur representation of the empirical likelihood quantile process. Journal of Nonparametric Statistics. 12, 645-665. Chen, J. and Shao, J. (2000). Biases and variances of survey estimators based on nearest neighbor imputation. Journal of Official Statistics. 16, 113-132. Chen, J. and Sitter, R. (1999). A pseudo empirical likelihood approach to the effective use of auxiliary information in complex surveys. Statistica Sinica. 9, 385-406. **[PROFESSIONAL CONSULTATION AND SERVICE]**

National Committee Membership Served on the Grant Selection Committee of the Natural Science and Engineering Research Council of Canada: 2000-2002. Served on the Committee of the Canadian Mathematics Competition: 1998-2001. Member of membership committee of International Chinese Statistical Association from Jan, 1998 - Jan 2000. **[EDITORSHIP]** Associate editor of the Canadian Journal of Statistics: Starting Februray 2002.

CHAN, Ivan Siu-Fung

[PRESENT POSITION] Associate Director - Scientific Staff at the Department of Clinical Biostatistics, Merck Research Laboratories, West Point, Pennsylvania. Dr. Chan has been with Merck Research Laboratories since 1995 after receiving his Ph.D. degree. **[DEGREES]** Ph.D. in Biostatistics (1995), M.S. in Biostatistics (1993), University of Minnesota; M.Phil. in Statistics (1991), B.S. in Statistics (1989), The Chinese University of Hong Kong. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Dr. Chan's research interests include exact inference, analysis of non-inferiority and equivalence trials, clinical trial methodologies in vaccines, and goodness-of-fit tests in sparse tables. **[SELECTED PUBLICATIONS]** Dr. Chan has published many papers in leading statistical journals such as Biometrics, Statistics in Medicine, The American Statistician, Statistical Methods in Medical Research, Computational Statistics and Data Analysis, and Communications in Statistics. He also has many publications in clinical journals including AIDS, The Journal of Infectious Diseases, Vaccine, The Journal of Pediatrics, and Pediatric Infectious Disease Journal. Dr. Chan has also co-authored three chapter entries (including one on vaccine clinical trials) for the Encyclopedia of Biopharmaceutical Statistics, 2nd Edition. **[ICSA ACTIVITIES AND OFFICES HELD]** Dr. Chan has been a member of ICSA since 1996. He currently serves on the Program Committee for the 2002 ICSA Symposium on Applied Statistics. He has also helped organize the first ICSA International Conference in Hong Kong in 1990, chaired a section at the 1998 ICSA Symposium on Applied Statistics, and made several presentations at these annual symposiums. **[RELATED PROFESSIONAL AACTIVITIES]** Dr. Chan is a member of the ICSA, American Statistical Association, International Biometric Society, and Drug Information Association. He currently serves as Associate Editor for Biometrics, an adjunct faculty member at Villanova University, and as Program Committee member and Session Moderator for the Deming Conference on Applied Statistics. In addition, Dr. Chan has given short courses and numerous presentations at professional meetings, universities, and the FDA. He also has served as referee for many statistical journals.

WANG, Yazhen

[PRESENT POSITION] Associate Professor, 9/1998-present, Department of Statistics, University of Connecticut. **[FORMER POSITIONS]** Associate Professor, 5/1998-5/1999, Assistant Professor, 9/1992-5/1998, Department of Statistics, University of Missouri-Columbia. [DEGREES] Ph. D. in Statistics, 1992, University of California at Berkeley. M.S. in Probability, 1987, East China Normal University. B.S. in Mathematics, 1985, East China Normal University. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** GARCH and diffusion modeling in financial engineering and computation finance, wavelets, change-points and function estimation, long-range dependence and self-similarity, signal and image processing, and order restricted statistical inferences. My research on wavelets and financial engineering and computation has been continuously supported by NSF and NSA. **[PUBLICATIONS]** Wang (1994). The limit distribution of the least concave majorant of an empirical distribution. Statistics and Probability Letter 20, 81-84. Wang (1994). Quantum Gaussian processes. Acta Mathematicae Applicatae Sinica. 10, 315-327. Wang (1994). A Bartlett-type adjustment for the likelihood ratio test statistic with an ordered alternative. Statistics and Probability Letter 20, 347-352. Wang (1995). The L_1 theory of estimation of monotone and unimodal densities. Journal of Nonparametric Statistics 4, 249-261. Wang (1995). Asymptotic expansions of the likelihood ratio test statistic with ordered hypotheses. Sankhy\={a} A. 57, 410-423. Wang (1995). Jump and sharp cusp detection by wavelets. Biometrika 82, 385-397. Wang (1996). Function estimation via wavelet shrinkage for long-memory data. Ann. Stat 24, 466-484. Wang (1996). A likelihood ratio test against stochastic ordering in several populations. J. Amer. Stat. Assoc 91, 1676-1683. Wang (1997). Fractal function estimation via wavelet shrinkage. J. Roy. Stat. Soc. B 59, 603-613. Wang (1997). Small ball problems via wavelets for Gaussian processes. Statistics and Probability Letter 32, 133-139. Wang (1997). Minimax estimation via wavelets for indirect long-memory data. J. Statistical Planning and Inference 64, 45-55. Wang (1998). Change curve estimation via wavelets. J. Amer. Stat. Assoc. 93, 163-172. Wang (1999). Change-point analysis via wavelets for indirect data. Statistica Sinica 9, 103-117. Chen, Y., Hewett, J., Wang, Y. and Johnson, J. (1999). A rank test for equality of two multivariate populations vs a particular ordered alternative. Computational Statistics and Data Analysis 29, 129-144. Wang (1999). An Overview of Wavelet Regularization. In Bayesian Inference in Wavelet Based Models (Vidakovic and M\"uller, eds.), pp 109-114, Springer, June 1999. Wang, Y., Cavanaugh, J. E. and Song, C. (2001). Self-similarity index estimation via wavelets for locally self-similar processes. Journal of Statistical Planning and Inference, vol. 99, pp. 91-110. **[ICSA ACTIVITIES AND OFFICES HELD]** Associate editor of Statistica Sinica

HSIAO, Chin-Fu

[PRESENT POSITION] Assistant Investigator, Division of Biostatistics and Bioinformatics, National Health Research Institutes, Taipei, Taiwan. Assistant Professor, National Taipei Nursing School, Taipei, Taiwan. **[FORMER POSITIONS]** Postdoctor Fellow, Division of Biostatistics and Bioinformatics, National Health Research Institutes, Taipei, Taiwan. [DEGREES] University of Wisconsin-Madison, Wisconsin, U.S.A.: Ph.D. in Statistics. National Central University, Taiwan, R.O.C.: M.S. in Mathematics. National Central University, Taiwan, R.O.C.: B.S. in Mathematics. **[FIELDS OF MAJOR STATISTICAL ACTIVITIES]** Sequential decision theory; Bayesian analysis; genetic study. [PUBLICATIONS] Ko, J-H, Lee, T-C, Hsiao, C-F, Lin, G-L, Liang, C-W, Chen, T-T, Wang, L-D, Chao, C-C, Yen, S-H, Chen, K-Y, Sheen, T-S, Hsiung, C-A, Chen, P-J, Hsu, M-M, and Jou, Y-S (2002). A comprehensive deletion mapping on chromosomes 3, 9, 11 and mutational screening of FHIT, p16INK4a, p19ARF genes in nasopharyngeal carcinoma. To appear in Cancer. Wu, K-D, Hsiao, C-F, Ho, L-T, Sheu, H-H, Pei, Dee, Curb, D., Chen, Y-D I., Tsai, H-J, Dzau, V. J., Cox, D., Tai, T-Y (2002). Clustering and heritability of insulin resistance in Chinese and Japanese hypertensive families: A SAPPHIRe sib study. To appear in Hypertension Research. Chang, I. S., Chen, M. Y., Hsiao, C. F., and Hsiung, C. A. (2002). A unified multipoint linkage analysis of qualitative and quantitative traits for sib-pairs. Statistica Sinica 12, 297-309. Hsiao, Chin-Fu and Clayton, Murray K. (2001). Bayes discrete sequential boundaries for clinical trials. Communications in Statistics: Theory and Method 30, 1381-1394. Hsiao, Chin-Fu and Clayton, Murray K. (2001). Lerche's sequential test for the drift of a Brownian motion with a smooth prior. Sequential Analysis 20, 183-189. Ranade, K., Wu, K.D., Risch, N., Olivier, M., Pei, D., Hsiao, Chin-Fu., Chuang, L.M., Ho, L.T., Jorgenson, E., Pesich, R., Chen. Y.D.I., Dzau, V., Lin, A., Olshen, R.A., Curb, D., Cox, D.R., and Botstein D. (2001) Genetic Variation in aldosterone synthase predicts plasma glucose levels, PNAS 98, 13219-13224. Chien-Ching Hung, Szu-Min Hsieh, Chin-Fu Hsiao, and Mao-Yuan Chen (2001). Risk of recurrent nontyphoid Salmonella bacteremia after discontinuation of ciprofloxacin as secondary prophylaxis in AIDS patients in the era of highly active antiretroviral therapy. AIDS 15, 645-655. Ranade, K., Chang, M. S., Ting, C. T., Pei, D., Hsiao, C. F., Pesich, R., Hebert, J., Chen, Y. D., Olshen, R., Risch, N., Cox and D. R., Botstein, D. (2001). High-throughput genotyping and mapping of single nucleotide polymorphisms. Genome Research 11, 1269-1274. Lin, Miao-Hsiang, Hsiung, Chao A. and Hsiao, Chin-Fu (1994). A program for monotonizing two empirical Bayes estimators in binomial and hypergeometric data distributions, Psychometrika 59, 423-424. **[RELATED PROFESSIONAL ACTIVITIES]** ICSA, ASA.

HO, Shu-Yen

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SPECIAL TOPIC — WEATHER

中國近 20 年來氣象統計預報綜述

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摘要

近 20 年來，多元統計分析方法有了長足的進步，湧現出不少新方法、新技術。本文著重介紹了近 20 年來氣象統計預報在中國氣象業務科研中的一些應用和發展，主要從多元統計分析意義上來選材。

關鍵字：多元分析、氣象統計、預報。

一、 前言

氣象統計預報在中國氣象業務預報和科研工作中佔有重要的位置，特別是在模式統計釋用及中長期預報業務中，統計預報更是扮演著一個重要的角色，多元分析中的回歸分析、典型相關分析、EOF 分析等更是氣象預報和分析不可少缺的工具。近 20 年來，氣象統計預報在中國取得了長足的發展。本文主要綜述統計方法在氣象預報業務中的各個方面的應用及其所取得的一些成績。

二、 多元統計分析在氣象預報業務中的應用

1、 回歸分析

廣東、江西、河北、遼寧等氣象局[1]用 0、1 權重回歸、逐步回歸、多元回歸等方法，得出晴雨 MOS 預報方程。1978 年曹鴻興等、史久恩等[2]用逐步回歸建立最高、最低氣溫預報方程。新疆自治區氣象臺張家寶等[3]以預報員經驗爲基礎，採用完全預報（Perfect Prog Method）方法,應用 0、1 權重回歸建立了有無寒潮的預報。上海氣象臺丁長根、黃家鑫[4]用逐步回歸建立 U、V 和 S（全風速）預報方程。1965 年 W.F.Massy[5]提出的主成份回歸、1970 年 Hoerl 和 Kennard[6]提出的嶺估計(Ridge estimate)以及 Webster 等人[7]提出的特徵根回歸(Latent root regression, LRR)對在回歸分析中出現複共線性(Multi-collinearity)有較好的處理。馮耀煌[8]在預報集成中,應用了嶺回歸技術,李耀先[9]用嶺回歸作水稻産量年景預測。魏松林[10]用特徵根回歸建立長春 6-8 月平均氣溫的特徵根回歸。

Furnialhe 和 Wilson 提出的窮盡所有回歸的演算法，比較徹底地解決了最優回歸（即最優子集回歸）的問題。張萬誠[11]用最優子集回歸作低緯高原雨季開始預報。

在氣象預報的實際工作中，常要考慮多個引數（預報因數）與多個因變數（預報量）的關係。中國數學家張堯庭[12]解決了這一問題的演算法，徐一鳴等[13]用多預報量雙重篩選逐步回歸作颱風路徑預報，嚴華生等[14]用多因變數多引數建立大氣環流--區域水稻産量預報。

引入非線性回歸是近年來發展的趨勢。馮耀煌等[15]、薑子俊等[16] 提出了一種選擇非線性最優預報因數和建立非線性預報方程的方法, 可用於長、中短期預報。

近年來由於數值預報模式的頻繁更叠，使模式輸出統計預報方法受到新的考驗，黃嘉佑等[17]介紹了卡爾曼濾波在天氣預報中的應用，劉春霞等[18]用此方法製作了廣東省冬季的最低氣溫預報。近年來，卡爾曼濾波技術在短期氣候預測中也得到了應用[19]。

2、 判別分析

廣東省徐聞氣象局[20]用二級判別做颱風登陸地段的預報。Fisher、Bayes 以及逐步判別等雖然在氣象實際中廣泛應用，但嚴格地說，這些方法僅當變數爲正態分佈時才可應用， Logistic 判別對變數的基本假設條件較寬，對未經正態檢驗的變數應用本方法是可行的，且可用於既有連續變數又有多值離散變數的情形。呂純濂等[21] 將 Logistic 判別引入中國氣象界，並研究了二次 Logistic 判別[22]分析及逐步判別[23]在氣象中的應用。

3、 相關分析

近 20 年來在氣象統計中用得較多的主要有典型相關（CCA）分析和奇異值分解（SVD）方法。CCA 是提取兩個氣象場的最大線性相關摸態的方法。朱盛明、祝浩敏[24]在數值預報的解釋應用中用典型相關分析提取有物理意義的預報因數作預報方程。陳嘉玲、謝炯光[25]用典型相關分析作中期冷空氣預報。黃嘉佑[26]用典型相關分析作副高的統計動力預報。近年來發展了一種新的 CCA 改進方法，稱爲典型相關分析的 BP（Barnert 和 Preisendorfer）方法，在氣象統計中也得到了應用[27]。

奇異值分解（SVD）也是提取兩個場的最大線性相關摸態的方法，SVD 方法可以變成是兩個要素場關係的擴大 EOF 分析。謝炯光等[28]用奇異值分解方法，求出了廣東省前汛期（4-6 月）西太平洋場海溫與廣東省降水場的 6 對奇異向量，來作汛期降水趨勢預報。江志紅等[29]用 SVD 方法討論了中國夏半年降水與北太平洋海溫異常的關係。

4、 氣象場的分解及其應用

50 年代中期由 Loreng 引入到大氣科學研究中的主成份分析以及後來發展的擴展經驗正交函數、複經驗正交函數、旋轉主分量分析、R 型、Q 型因數分析、對應分析、主震蕩型（Principal Oscillation Parterns, PPOS）。使氣象研究及業務水平進入一個更高層次。

4·1 經驗正交函數（EOF）分解

章基嘉等[30]應用經驗正交函數對亞洲 500hPa 侯平均環流與我國侯平均氣溫之關係的時空結構進行分析。用 EOF 逐年劃分自然天氣季節，張邦林、醜紀範[31]提出了一種時空綜合的經驗正交函數分析方法，多數的經驗正交函數分解是在標量場上展開的，但風場也用經驗正交函數展開，周紫東等[32]、王盤興[33]討論了氣象向量場的經驗正交函數展開方法及其應用。

4·2 主成份（主分量）分析及其因數分析

氣象分析預報中，常要分析許多變數，而變數間往往互有影響，如何從多個變數中找出很少幾個綜合性的指標代替原來較多的指標，而且所找到的綜合指標又能盡可能多地反映原來資料的資訊，而且主成份之間又是相互獨立的主成份分析。

何敏等[34]用主分量研究了歐亞地區大氣環流年際振蕩的時空分佈特徵，謝炯光[35]用主分量與非線性降維和相似綜合作廣東月降水量分佈預報，陳創買等[36]提出一種氣候場的主分量逐步回歸預報模型，該模型將氣候場的預報變成對氣候場主分量的預報，並通過相關分析和逐步回歸，求得氣候場的主分量與各種不同的因數場的主分量因數之間的聯繫。用於廣東年降水的預報。

4·3 擴展經驗正交函數（EEOF）

1982 年 Weare 和 Nasstrom[37]提出的 EEOF 分解可以得到氣象場空間分佈結構，也可以得到隨時間變化空間分佈結構的變化。張先恭等[38]用 EEOF 做太平洋海表溫度與中國降水准 3.5 年周期變化。

謝炯光[39]提出一種月、季降水預測的新方法，用 EEOF 分解得到的前期特徵向量場，來預測後期的降水場分佈特徵。

4·4 複經驗正交函數（CEOF）

Rasmusson 和 Barnetl 提出的複經驗正交函數（CEOF）[40]能表現出氣象場的位相變化及空間傳播特徵。

黃嘉佑[41]使用複經驗正交函數分析中國降水長期變化的准兩年周期振動，魏鳳英等[42]用 CEOF 分析了近百年中國東部旱澇的分佈及其年際變化特徵，符綜斌等[43]曾將 CEOF 分析用於 Elnino 增暖的振幅和位相變化，畢慕瑩[44]用 CEOF 分析研究了夏季西太平洋副高的振蕩。

4·5 因數分析、旋轉主因數分析（RPC）

將主成份分析向前推進一步，就是因數分析，因數分析又分 R 型分析和 Q 型分析兩種，我們知道，由於主因數是通過原始變數的線性組合得到的，因而可以瞭解到其天氣意義。但哪一個主因數的天氣意義更重要些，可通過因數荷載矩陣進行分析，一般來說因數荷載矩陣越簡單越易解釋。爲此，使每個因數的荷載平方按列向 0 或 1 兩端分化。使主因數在每個變數上的荷載趨近於 1，而在其他變數上的荷載接近於 0，這樣，就更容易解釋主因數的天氣意義。這種變換稱爲旋轉主因數分析，一般分正交旋轉與斜交旋轉兩種方式。極大方差旋轉是正交旋轉，是氣象預測、科研業務中最常用的旋轉方法。謝炯光等[45]用因數分析和旋轉因數分析對西太平洋 8 個海區進行了分析，對頭 4 個主因數的物理意義進行了初步的解釋，進而用它建立了廣東省各月降水與海溫的預報方程。黃嘉佑[46]用斜旋主分量分析了我國夏季氣溫及降水場（1951-1987 年）的時空特徵，王敬方等[47]用旋轉主分量（RPC）方法，分析近 40 年來我國夏季溫度變化的規律。

4·6 對應分析

對應分析是一種綜合了 R 型及 Q 型因數分析特點的多元統計分析技術，黃嘉佑[48]、李麥村等[49]用該方法發現副高逐月變化曲線與赤道海溫變化十分相似，謝炯光[50]用對應分析對 4-6 月逐月的連續變化進行分型，把各月的降水連續變化分爲連升型、連降型、降後升型等四型，並利用回歸分析作出各型的預報，在前汛期降水趨勢和冬半年（1—3 月）氣溫趨勢的預測中收到了較好的效果。

4·7 主振蕩型（POP）分析

主振蕩型（POP）是 Hasselmamm 和 Storch 在 20 世紀 80 年代末提出來的[51]。章基嘉等[52]對離散化場時間序列推導了主振蕩型分析方法的兩個導出量：主振蕩型（POP）及其伴隨相關型（ACP）。通過熱帶太平洋 SST 矩平場時間序列 POP 及相應區域 850hPa 風場 ACP 的計算例子，給出了它們的實際演算法。

5 聚類分析

鄭祖光[53]在首先不能確定用幾個因數和分成幾類的情況下，提出用變 K 變 N 方案。章基嘉等[54]應用 K-均值聚類法對東亞各自然天氣季節 500hPa 平均環流進行分型試驗。在聚類分析中多數的分類樣品是相互獨立的，分類時彼此是平等的，但在一些問題中，樣品的分類是不能打破順序的。比如，對某一階段氣象要素資料進行分段以確定不同時段的氣候特徵。這種分類，稱爲分割更爲形象一些， Fisher 提出了最優分割的演算法，謝炯光等[55]利用最優分割，對中國 T106 數值預報輸出產品的各種物理意義明確的預報因數進行最優二分割，挑選出晴雨及有無大於 25 毫米降水的預報因數，建立概率回歸方法，做 24-144 小時的晴雨，大於 25 毫米降水的完全概率預報，在業務中收到較好效果。最優二分割的進一步優化，產生了一種叫做 AID 的分割演算法（Automatic Interaction Detection），利用 AID 方法，不但可以分類，還可以根據新的樣品落區在哪一類作出預報。AID 具有解決一些非線性問題的能力。謝炯光等[56]據天氣學實踐選出 47 個與廣東省颱風、暴雨關係密切的預報因數，利用 AID 方法，進行計算做出颱風暴雨的短期預報。

6 譜分析

6·1 功率譜

李小泉等[57]利用譜分析研究 500hPa 環流指數的變化，譜分析也常常與其他方法相結合應用於天氣分析與預報中，黃嘉佑[58]在研究海溫場與太平洋副熱帶高壓之間的關係時使用交叉譜發現，海溫不單有明顯的兩年振動周期，而且這種振動存在於太平洋地區的氣壓系統中，關係十分密切，它們

之間的凝譜平方值高值 0.65 的臨界值。符淙斌[59]利用協譜與正交譜研究緯向和經向垂直環流強度之間的反相耦合振蕩關係。

6·2 **最大熵譜分析**

在連續功率譜估計中，自相關函數估計與樣本量大小有關，1967 年 Burg 提出了一種稱之爲“最大熵”譜估計的方法，具有解析度高、適用於短序列等優點。繆錦海[60]討論了最大熵譜的優良特性和預報誤差過濾下係數階段的確定。曹鴻興等[61]討論了氣象歷史序列的最大熵譜分析。魏鳳英[62]用最大熵譜提取 1952-1995 年華北地區春季乾旱指數序列的顯著周期。

6·3 **奇異譜分析（SSA）**

奇異譜分析(Singular Spectrum Analysis)是從時間序列的動力重構出發與經驗正交函數(EOF)相結合的一種統計分析技術，特別適合用於大氣的非線性振動。吳洪寶[63]、劉健文等[64]系統介紹了奇異譜的原理及其在氣象中的應用。謝炯光等[65]用 SSA 方法對登陸廣東省的熱帶氣旋的演變規律進行了分析，發現年登陸廣東的熱帶氣旋存在明顯的 8 年，准 3 年的周期振蕩，登陸珠江口以西的熱帶氣旋，存在 12 年，准 2 年的振蕩周期。

6·4 **小波分析**

小波分析是從傅立葉分析方法發展起來的並被認爲是傅立葉分析方法的突破性進展。戴新剛和醜紀範[66]用子波變換研究了長江和黃河流域徑流的周期性問題，紀忠萍等[67]用小波分析對廣州近百年來氣候變化的多時間尺度進行分析，紀忠萍等[68]用小波變換分析廣東省低溫陰雨的年景趨勢變化，著重分析了重低溫陰雨年在小波係數圖中的分佈特徵，並根據分析結果對未來 1-2 年的低溫陰雨年景進行了預測估計。

7 時間序列分析模型

在氣象上用得較多的主要有自回歸模型（AR）、滑動平均模型(MA)、自回歸滑動平均模型（ARMA）、自回歸求和滑動平均（ARIMA）模型。氣象要素的時間序列多數是屬非線性變化的，上述的時間序列建模模型均爲線性模型。而時間序列分析中的門限自回歸模型（TAR）是一種非線性模型，它利用逐段線性化手段來處理非線性系統。由於門限的控制作用，保證了遞推的穩定性。門限自回歸模型可以有效地描述非線性振動現象，可以解釋自然界各種類型的穩定迴圈。丁裕國等[69]利用奇異譜分析對 Nino 海區 SSTA 月際序列作短期氣候預測試驗，採用 AR(P)模型，結果發現在 SSA 分析基礎上的 AR 模型對 ENSO 海區的 SST 預報特別有效。史久恩等[70]用自激勵門限自回歸模型作 SOI（南方濤動指數）的預報，其結果與線性 AR 模型相比較，結果表明非線性門限自回歸模型擬合 SOI 資料，比線性模型更能有效地反映資料的內在規律。

8 多層遞階方法

1983 年中國韓志剛教授[71]提出了建立在現代控制理論中“系統辨識”基礎上的含時變參數的新型統計預測方法—多層遞階方法。這種時間序列的新預報方法在氣象預報服務中取得了較好的效果[72]，不少學者在使用過程中對這種方法的應用方面作了進一步的改進，使其在氣象預報應用上得到進一步的提高[73]。

9 均生函數模型

曹鴻興、魏鳳英等提出了時間序列的均值生成函數（Mean Generating Function, MGF,簡稱均生函數）模型。均生函數預測模型既可以作多步預測，又可以較好地預測極值，爲短期氣候預測開闢了一條新的途徑。魏鳳英、曹鴻興[74]在《長期預測的數學模型及其應用》與《現代氣候統計診斷預測技術》兩書中對均生函數模型的數學原理及其在氣象中的應用作了詳細的介紹。

10 灰色系統預測模型

“灰色系統”理論，是我國學者鄧聚龍教授提出的新型理論。到目前爲止，人們對天氣（氣候）系統的演變規律、發生、發展、消亡機制，子系統間的相互作用的瞭解尚不清楚、不充分，限制了動力和統計方法對天氣（氣候）系統的深入研究。天氣氣候系統，由於其複雜性，是一個典型的部分資訊已知和部分資訊未知的灰色系統。因此，鄧聚龍教授提出的灰色系統理論爲氣象預測和分析研究提供了一個有力的工具。曹鴻興、翁文潔等人對灰色分析與預測及其在氣象中的應用作了推廣[75]，鄧聚龍[76]在“灰色預測與決策”一書中對灰色系統的理論的來龍去脈，具體計算方法作了詳細的介紹，並把 GM(1,1)模型、災變預測、季節災變預測、拓撲預測等方法在氣象中的實際應用作了介紹。謝定升等[77]根據 GM(1,1)模型的方法原理，作降水峰日的中期預報。

11 車貝雪夫多項式展開

經典車貝雪夫多項式展開只適用於矩形網格，周家斌將車貝雪夫展開推廣到不規則格點上，並將其用於氣象要素的分佈預報[78]。周家斌提出了一種用車貝雪夫多項式做時間序列預報的叠代演算法，這是一個非線性、非參數方法，無需對序列作平穩或其他假定。它的擬合和實際預報效果較好[79]。

12 神經網路原理在氣象中的應用

近年來神經網路在氣象中的應用快速發展。周曾奎等[80]利用神經 BP 網路模型輸出判斷颱風移向趨勢－西進、北上、西北移。於波等[81]結合模糊判斷技術利用多層神經網路對 GMS 雲圖的台風雲系進行圖像識別。謝炯光等[82]利用神經 BP 網路進行月雨量集成預報試驗，金龍等[83]提出了小波變換與神經網路相結合的多步預測模型。

13 非線性動力學

林振山[84]首先提出了諾幹相空間預報模型，並提出將相空間模處理組合法用於業務預報中。周家斌[85]提出了相空間向量相似方法，相軌迹變率方法，空間變換方法和相空間模方法等 4 種以混沌理論爲基礎的預報方法，這些方法已經用於南方濤動強度、北京降水和華北降水分佈的預報。

14 分形

近年分形的思路和方法正逐步在氣象分析和業務中得到應用。劉式達等[86]指出分數維是氣候系統結構的特徵，是氣候系統中尺度變換後的不變數。付昱華[87]應用分形分佈模型 N=C/rD 的推廣形式，即連續變維分形（分維數 D 是 r 的連續函數，而不是常量）預測颱風路徑。

三、 結束語

近 20 年來統計氣象學在中國取得了長足的發展，統計預報在中國氣象業務預報和科研中佔有重要的位置。主要表現在：

1 在數值預報產品統計釋用中，統計預報方法發揮了積極的作用。

2 隨著計算技術和電腦的發展，以場分析和場相關的統計預報方法如 SVD、EEOF、CCA 分析等方法得以在業務上得到了廣泛應用，對提高業務預報精確率幫助很大。

3 一些新的統計方法由於種種原因，用在氣候分析中較多，用在業務預測上較少，有待今後進一步開發。

4 近年來國內外一些數學界的研究新成果，如自記憶方程、主振蕩模、混沌分形、小波分析等引入到氣象界的速度很快，如何使其在天氣預測中更快、更好地發揮作用值得研究。

5 在統計預報的使用中，如何發揮統計預報的長處，避免其不足的地方，要繼續研究。

參 考 文 獻 （略）

對本文所列的參考文獻有興趣的讀者，歡迎向作者索取。

!!! Controversial !!!
Statistical
Issue

Bridging Studies

Implementation of Bridging Strategy in Taiwan

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Introduction

Recently, with the advance of human genome decoding and pharmacogenomics, issues on ethnic and population differences have taken the center stage in the new drug approval process. Since most of the new medicines were developed in western countries, the efficacy and safety of a drug was generally established based on Caucasian majority. Whether the foreign clinical data could be naively extrapolated to the population of a new region would be a major concern, especially in Asia. In March 1997, a consensus has been reached for ICH-E5 (1). The guidelines address both the intrinsic and the extrinsic factors that are associated with drug characteristics, culture and environment; and provide a framework for evaluating the impact of ethnic factors upon the medicines' effect. The principal objective of E5 is to expedite the global development and availability of new medicines to patients without sacrificing the quality, safety and efficacy. While minimizing duplication of clinical studies, the guidelines also facilitate the use of bridging studies to allow extrapolation of foreign clinical data to a new region. Since the introduction of ICH-E5 and the bridging concepts, awareness has increased among nations about the need for local clinical trials. Many Asian countries including Japan, Korea, and Taiwan, have formally announced the implementation of the bridging study requirement. Other Asian countries are also showing great interest in setting up a well-designed bridging study system.

In order to create a united Asian market under the harmonized regulatory system, Taiwan is leading and promoting the "APEC (Asian Pacific Economic Cooperation) Network of Pharmaceutical Regulatory Science - APEC Joint Research Project on Bridging Study". Two regional workshops were held in Taipei in 2000, and 2001. Scientific data related to ethnic factors were reviewed systematically in the meetings. With the help from CDE (Center for Drug Evaluation), the Department of Health has successfully developed a sponsor self-evaluation check-list, a decision-making tree, and consultation procedures (see CDE Website at<www.cde.org.tw>) . As well, the Department has planned educational workshops and set up a statistical working group. Requirement of a possible bridging study was formally announced on Dec. 12, 2000, giving a 2-year transition period (until Dec. 12, 2002) to phase out the current local registration trial requirement.

Evaluating the necessity of a bridging study

In general, Taiwan accepts all Asian data. A study by Lin et al. in 2001 (2) found that the so-called "Taiwanese", accounting for 91% of the total population in Taiwan, is comprised of Minnan and Hakka people who are closely related to the southern Han, and are clustered with other southern Asian populations in terms of HLA typing. Those who are the descendants of northern Han are separated from the southern Asian cluster, and form a cluster with the other northern Asian populations. As the Taiwanese regulatory authority acknowledges the trial data conducted in Taiwan regardless of the ethnic origin of the subjects, it will acknowledge all Asian data as well.

From the regulatory point of view, ethnic factor should not be defined completely by "Citizenship" or "Race". In the evaluation of ethnic differences, "Drug Characteristics" and "Indication" are the two fundamental elements to be considered. For example, some medicines are metabolized by enzymes with genetic polymorphism. If there is a higher percentage of poor metabolizers in Taiwanese patient population for a particular drug, adjustment of the claimed marketing dose may become necessary. Usually, hepato-toxicity is a major safety concern in bridging assessment. Due to the high prevalence rate (18%-20%) of HBsAg carriers in Taiwan, the need for more experiences with the usage of liver toxic agents in hepatitis B or C carriers may lead to the necessity of an additional bridging study. Difference in disease epidemiology and disease manifestations is another important issue. As illustrated in the case with female postmenopausal syndrome, Caucasian women usually present more vasomotor symptoms in contrast to Taiwanese women in whom vasomotor symptoms are not predominant (3). Therefore, new agents whose efficacy was demonstrated by improved Kupperman Index score (which is weighted on vasomotor symptom domain) may not be accepted outright. Further investigations on Taiwanese postmenopausal women, using an index scale more suitable for this population (i.e., Greene Climacteric Scale) may be needed. Furthermore, medical practice between regions usually reflects one of the greatest variation and is the most difficult to harmonize. Differences in diagnostic criteria for some diseases, potential of drug abuse and possible drug-drug interactions are all essential considerations in evaluation for bridging studies.

In the past, little Asian clinical data were provided with the clinical data package used for new drug registration in Taiwan. Statisticians usually made no contribution in the bridging assessment since no information could be obtained from such limited data points. In some situations, PK profile obtained

from a small number of Asian subjects might be presented. For such cases, the point estimate, 95% confidence interval and the corresponding descriptive plot for each PK parameter might be compared among ethnic groups by scientific judgement rather than a formal statistical procedure. Recently, in compliance with the ICH E5 and the regional needs for Asian data, as well as a good clinical research infrastructure being set up in the Asian regions, more and more industry sponsors have agreed to involve Asian populations in global R & D trials, i.e., early phase IIIa trials. For a concurrently performed multinational, multicenter phase III trial including Asian clinical sites as study centers, the "consistency trial" approach by Shih (4) may be applied to the evaluation of the bridging evidence. In some particular cases, an early phase III trial is performed completely on Asian population, using an identical protocol as the concurrently ongoing Caucasian trial. For such cases, conventional meta-analysis by pooling the data from two or more trials may be utilized to detect the heterogeneity between and/or among patient populations.

Designing a bridging study

The acceptance of foreign clinical data will depend completely on its ability to be extrapolated to Taiwanese population. When this is in doubt, supplemental bridging data may be requested by the regulatory authority. In general, bridging study could be widely applicable to trials of any phase, including pharmacokinetic and pharmacodynamic studies, and phase III controlled clinical trials. However, a phase III controlled clinical trial is preferred because it is the most favorable study when there are uncertainties about dose, when there is limited experience with the drug class, or when there are safety concerns.

Ideally, a bridging phase III trial should have a study design identical to the foreign pivotal study. However, a full phase III clinical trial may not be practical considering small individual market in the local region. To remedy this and to accelerate the approval of a good medicine to be marketed in Taiwan, several compromising strategies are proposed. For example, we may allow the widely accepted surrogate endpoints to serve as primary efficacy endpoints, i.e., bone density in place of bone fracture in osteoporosis trials and objective tumor response rate in place of patient survival in cancer trials. Under some circumstances, the study period may be shortened if clinically justifiable. Though a sample size computed to powerfully address similar efficacy and safety to those of pivotal studies is scientifically more sound, it is to our knowledge that the calculated sample size is often too large to be practical. Alternatively, a positive drug effect (d_N) in Asian population is thought to be sufficient in sample size justification given that the effect of the original pivotal studies (d_O) has been shown positive, and, dN is within an acceptable range of d_O (5). In terms of significance level and power used in computing required sample size, we consider protecting only the type I error. The one-sided alpha level could be relaxed with an upper bound of 10%. As for the power, we deem it the sponsor's responsibility.

Conclusions

The new requirements for bridging study have ushered a new paradigm for regulatory approvals in Taiwan. Previous administrative formality such as the requirement of small-scale local registration trial for all drugs and free sale certificates will be gradually phased out. However, to draw a statistical inference with regard to bridging evidence by comparing two extremely unbalanced samples (i.e., size 20:1) of two patient populations from a single trial, or two separate studies is nontrivial. The statistical work on this field is still in a preliminary stage. We encourage all ICSA members to join us in settling these interesting and challenging issues.

Perhaps what is more important than the specifics of our statistical approach is that all pharmaceutical parties worldwide should work collaboratively in the process of new drug development. We would emphasize that "bridging study" is only a transitional strategy. We believe that with accumulated empirical experiences over time, bi-directional extrapolation (Asian data being extrapolated to European population and vice versa) for several classes of drugs will become a reality and, therefore, additional local clinical trials will not be needed.

With the implementation of ICH E5 accompanied by practice of good regulatory sciences, great opportunities exist for Taiwan to participate in the global R & D and to establish sound IND consultation process. These efforts will ultimately benefit the health of Taiwan populations.

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Overview of Statistical Issues for Bridging Studies

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In 1990, the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) [4] was initiated with the goal of harmonizing the requirements for discovery, development, and approval of new medicines across different geographic regions. Regulatory agencies from three regions: Europe, Japan, and the United States, collaborated with leading experts from the pharmaceutical industries in each region in this initiative. The primary objectives of the ICH were to provide guidelines that would avoid unnecessary repetition of costly and time-consuming clinical trials and thus facilitate and expedite, without sacrificing safety or quality, approval of new medicines in different global regions.

The publication of ICH-E5 [5] in 1998 provided guidelines for evaluating the impact of ethnic factors on the safety, efficacy, dose, and dose regimen of a drug under development and to identify those drugs whose characteristics make them more or less likely to be sensitive to differences in ethnic makeup. Ethnic factors include those that are intrinsic, such as genetic factors, race, weight, and other physiological characteristics, as well as those which are extrinsic, including environmental factors such as climate, pollution, and medical practice. Properties of a compound which predispose it to be less sensitive to ethnic factors include linear pharmacokinetics, a flat exposure-response curve for efficacy and safety at a given dose and regimen, a wide therapeutic dose range, minimal metabolism distributed among multiple pathways, high bioavailability, low potential for protein binding or interactions with other drugs or diet, and low potential for inappropriate use. Properties which would indicate that a compound is more likely to be ethnically sensitive include non-linear pharmacokinetics, metabolism through a single pathway, metabolism by enzymes known to exhibit genetic polymorphisms, a highly variable bioavailability between subjects, low bioavailability, a high likelihood of use with other medications, and a high likelihood of inappropriate use.

These guidelines provide loose criteria but do not provide clear scientific quantification of characteristics or thresholds of differences beyond which ethnic sensitivity would be assumed. A review of the literature in the Medline and Current Index to Statistics (CIS) databases shows that, although several authors have articulated many issues that need to be considered in global drug development, in general these expositories stop short of offering specific statistical methodologies. [3,6,11]

Thus, it is incumbent on the statistical community to collaborate with medical professionals to develop criteria for identifying the thresholds and statistical tests for establishing whether such thresholds have been crossed. The statistical community is also charged with developing appropriate designs for bridging studies and appropriate analysis methodologies for data from such studies.

Quantitative methods to be used for global drug development must address pharmacokinetic endpoints, pharmacodynamic outcomes of efficacy and safety, and the exposure-response relationship. These endpoints may be continuous, ordinal, dichotomous, or time-related and distributions of these endpoints may be normal, skewed, or bi-modal.

There are several considerations which will determine the appropriate direction for statisticians. First, the typical goal of bridging studies, as explicitly stated in ICH-E5, is to demonstrate that the properties of the drug are similar, rather than different, across global regions. Thus, with the goal of showing that the pharmacokinetics, efficacy, and safety of the drug are similar between global regions, tests of equivalence may be more appropriate than standard hypothesis tests. Within the equivalence framework of hypothesis testing, acceptance of the alternative hypothesis allows one to conclude that the regions are the same within a predefined amount (e.g., 20%). However, if the alternative hypothesis cannot be accepted, the resulting confidence interval can be used to place the comparator region on the scale of the previous safety, efficacy, and exposure findings in the reference region. Within the standard difference framework of hypothesis testing, rejection of the alternative hypothesis (regions are different) does not allow one to conclude that the regions are the same (the null hypothesis). Because these studies are powered to detect differences of a certain magnitude in this standard framework, this could result in an increased number of false-negative findings of small but important regional differences. Tests for bioequivalence of pharmacokinetic parameters are well developed and accepted. Therefore, a natural component to a global drug development program might be to conduct studies with pharmacokinetic sampling in multiple ICH regions and develop sample sizes to detect equivalence between pharmacokinetic parameters across regions. With the growing use of non-linear mixed effects modeling (NONMEM"), the pharmacokinetic parameters could be obtained from Phase I studies in healthy volunteers with extensive sampling or a Phase II study in a representative patient population with sparse sampling. Further statistical methodologies are needed to address the issue of establishing equivalence between ICH regions with respect to efficacy and safety outcomes.

Ideally, domestic and foreign studies would be conducted simultaneously using a sampling strategy designed to obtain valid data for the estimation of pharmacokinetic parameters and for the assessment of efficacy and safety endpoints. For example, a parallel-group design stratified by region and by subgroups within region could be powered to simultaneously compare a new drug to a placebo both within and between geographic regions while allowing for unequal group sizes so that countries with economic or societal constraints could enroll fewer patients.

Such studies might be designed to assess the impact of regional differences in the pharmacokinetics of a drug and in toxicities as proposed by O'Neill. [8] O'Neill proposes modeling the hazard of adverse events as functions of time-dependent pharmacokinetic parameters such as cumulative AUC, along with other patient covariates that may be different with respect to region, in a model such as Cox's proportional hazards model [1] This approach appropriately accounts for the fact that adverse events

occur over a varying period of time and may be associated with exposure measures which also may vary over time. Patient characteristics in different ICH populations are thought of as covariates that take on different values for different types of patients, and the assumption is that patients in both regions have the same, albeit unknown and unspecified, underlying baseline risk of adverse events. If such an assumption is reasonable, then tests for interactions between exposure covariates and region-specific patient characteristics can be used to assess whether the exposure-toxicity relationship between patients in different regions is similar or different. For the simplest case, where toxicity can be defined as dichotomous (present or absent) and with an ethnic factor (present or absent) and a drug regimen (A or B), O'Neill proposes methodology to estimate the required sample size for detecting interactions between the ethnic factor and drug regimen of a pre-specified magnitude. Similar methodology would need to be developed to estimate the necessary sample size for assessing interactions between the time-dependent exposure measures and time-dependent toxicity outcomes as described above.

Often the manufacturer of a compound will conduct extensive studies in the region of origin only, and then, after these studies have proven the compound to be efficacious, seek global registration and marketing. It should be pointed out that there is a distinction between determining sample size for bridging studies that are conducted in a specific region after efficacy has already been shown in another region and those that are conducted concurrently in several geographic regions. In both cases, one would seek an appropriate sample size for the bridging study such that the study would be powered to detect equivalence using some predefined criteria, as is typically done in Phase I studies. However, it is necessary to recognize that, for tests of hypotheses comparing an historical group with one yet to be studied, the derived power function is random only through the region that has not yet been observed. Statistical methods for designing studies using historical controls have been developed for dichotomous [7] and survival time [2] endpoints utilizing the standard framework of hypothesis testing. However, these methodologies would need to be modified to detect equivalence rather than differences across regions, and new methods for continuous and ordinal outcomes would need to be developed.

An alternate methodology for designing a bridging study after substantial evidence of efficacy has been observed in several multi-center studies is proposed by Shih [9]. Shih argues that complete duplication of results in a new region is not essential provided one is reasonably confident that the results will be consistent with those already observed in other regions, and he also acknowledges that showing equivalence rather than difference is the ultimate goal of a bridging study. He proposes the idea of a "consistency trial" design based on Bayesian prediction whereby results from each previous study are used to construct a predictive probability distribution for specific results in the study for the new region. Criteria for concluding consistency are provided, along with sample size formula for normally distributed and binary outcomes. Such an approach is intuitively appealing and raises the point that the underlying goal of a bridging study is to show consistency, reproducibility, or equivalence in pharmacokinetics and pharmacodynamics of a drug between two regions.

In comparing pharmacokinetic parameters between patients in different regions, issues regarding skewness of distributions, different variabilities, and different measurement methods must be considered. The populations in different ICH regions may be so substantially different that statistical models which treat regional characteristics as different levels of a covariate may not be appropriate. Therefore, parametric assumptions may be more difficult to make in bridging studies and the use of nonparametric methods should be considered. One appropriate test for comparing pharmacokinetic parameters such as AUC between two populations is the Kolmogorov-Smirnov two-sample test [10]. However, much more complex differences in distributions can occur which would not lend themselves to this type of statistical test. For example, when drugs are metabolized by P-450 enzyme systems the underlying pharmacokinetic parameter distributions may have bimodalities, and the predominant mode may be different in different regions. Therefore, other statistical methods will need to be developed to handle such situations.

In summary, there are multiple tasks at hand for statisticians in the design and analysis of appropriate global drug development studies. This commentary identifies some of the issues and complexities that statisticians must consider. The existing methodologies proposed to date are a beginning, but much work remains.

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BRIDGING STUDIES: Is a bridge too far?

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I. Introduction

For marketing approval of a medicine, sponsors are required to provide substantial evidence of effectiveness and safety from adequate and well-controlled clinical trials. The U.S. Food and Drug administration (FDA) recommends that at least two clinical studies (the so-called pivotal trials) in the same targeted patient population be performed to confirm the reproducibility of evidence on efficacy, safety, and dose response. However, after a medicine is approved by the original region (e.g., the United States of America), sponsors might seek registration of the product in a new region (e.g., Asian Pacific countries). The possible differences in ethnicity and clinical practice between the regions and their impacts on the safety, efficacy, dose and dosing regimen have limited the willingness of the regulatory authority in the new region to accept the clinical data generated in the original region. Consequently, the regulatory authority in the new region often requests the sponsors to repeat studies for obtaining all or much of the clinical data in the new region. This extensive duplication of clinical evaluation in the new region not only demands valuable development resources but also delay availability of the new medicine to needed patients in the new region. To resolve this dilemma, the International Conference on Harmonisation (ICH) has recently published a tripartite guidance entitled "Ethnic Factors in the Acceptability of Foreign Clinical Data" to address the above issues [1].

The objective of the guidance is to provide a framework for evaluation of the impact of ethnic factors on the efficacy and safety of a medicine at a particular dosage or dose regimen. In addition, it describes regulatory strategies of minimizing duplication for clinical data and requirement of bridging evidence for extrapolation of foreign clinical data to a new region. In general, the types of bridging studies required depend upon the ethnic sensitivity of the medicine, experience of the drug class, extrinsic ethnic factors and ethnic differences between the new and original regions. From ICH E5 guidance, the following table is a summary of types of bridging studies with respect to the above-mentioned factors:

Medicine	Region	Medical Practice	Drug Class	Clinical Experience	Bridging Studies
Insensitive	–	Similar	–	–	No
Sensitive	Similar	–	–	Sufficient	No
Sensitive	Dissimilar	Similar	Familiar	–	PD
Choice of Dose	–	Different	Unfamiliar	Insufficient	CCT

From the above table, there are at least two fundamental issues in the ICH E5 guidance: (a) sensitivity of medicines to ethnic factors, necessity of a bridging study, and the nature and type of bridging studies, and (b) assessment of similarity based on bridging evidence.

II. Ethnic Sensitivity, Necessity of Bridging Studies, and Type of Bridging Studies

The ICH E5 guidance lists properties of a compound for assessment of sensitivity to ethnic factors: linear pharmacokinetics (PK), flat pharmacodynamic (PD), therapeutic range, degree of metabolism, extent of bioavailability, potential for protein binding, potential for interactions, genetic polymorphism, inter-subject variability, systemic mode of action, and potential for inappropriate use. However, the ICH E5 guidance also points out that no one property of the medicine is predictive of the compound's relative sensitivity to ethnic factors. Because of complexity due to possible interaction among drug's pharmacological class, indication, and demographic of patient population, the ICH E5 does not provide a precise and definitive criterion for evaluation of ethnic sensitivity. As a result, no probability statements can be made for the errors resulting from the decision-making on sensitivity to ethnic factors. Therefore both regulatory authority in the new region and the sponsor do not have a criteria and a method for an objective and impartial evaluation of ethnic sensitivity and necessity of a bridging study.

On the other hand, there are thousands of medicines that were approved for various indications for different patient populations by various regulatory authorities in different geographic regions, e.g. the U.S. Drug Master File. Sufficient pre-approval and post-marketing experience on the above-mentioned properties for ethnic sensitivities and impact of intrinsic and extrinsic factors on efficacy, safety, dosage, and dose regimen have been accumulated for these medicines. An instrument can be developed for three domains. The first domain includes the basic properties of the compound mentioned above, The second domain consists of intrinsic factors mentioned in Appendix A of the ICH E5 guidance. Domain 3 is constituted of the extrinsic ethnic factors mentioned in Appendix A of the ICH E5 guidance. Within each domain, a scoring scheme for each property or factors is designed to represent the degree of impact on efficacy, safety, dose and dose regimen. A possible scheme is a 5-point system, 1 (no), 2 (mild), 3 (moderate), 4 (strong), and 5 (complete). Then an algorithm can be formulated to provide a summary index for an overall assessment of impact of the medicine on efficacy, safety, dosage, and dose regimen. These thousand compounds can be divided into two sets: training set and validation set. Based on the summary indices computed from the medicine in the training set, a threshold can be determined to class these medicines into the group with no need of bridg-

ing studies and the group that bridging studies are necessary. Based on validation set, the probability of classification error can then be estimated. Within the group with the necessity for bridging studies, further cutoff points can be estimated for different types of bridging studies. When a new medicine is applied for registration in the new region, regulatory authority in the new region and sponsor can calculate this summary index to decide whether a bridging study is needed and what type of the bridging study is warranted. However, the above-mentioned task requires a joint and collaborate effort from clinicians, pharmacologists, pharmacokineticists, medicinal chemists, biostatisticians, medical informatics and behavior scientists.

III. Assessment of Similarity Based on Bridging Evidence

According to the ICH E5 guidance, a bridging data package consists of (a) selected information from the Complete Clinical Data Package (CCDP) that is relevant to the population of the new region, and (b) if needed, a bridging study to extrapolate the foreign efficacy and/or safety data to the new region. In other words, bridging evidence is actually provided either in the CCDP generated during clinical drug development program for submission to the original region or in a bridging study conducted in the new region after the pharmaceutical product is approved in the original region. When the bridging evidence provided in the CCDP can not allow extrapolation of foreign clinical data to a new region, then a bridging study should be conducted in the new region to generate a limited amount of clinical data to bridge the clinical data between the two regions.

Although the ICH E5 guidance clearly states that assessment of the ability of extrapolation of the foreign data rely on the similarity of dose response, efficacy, and safety between the new and original regions, either with or without dose adjustment, it does not provide a precise definition or criteria for evaluation of similarity. A direct interpretation of the ICH E5 guidance on similarity requires performing a between-region (study) analysis to evaluate the treatment-by-region interaction. It is then very clear that the sample size required for the test based on the treatment-by-region interaction will be much larger than that for detection of the treatment effect alone [2]. This statement is true for all types of studies and for all types of endpoints. On the other hand, one only wants to verify whether the evidence of efficacy or safety or PK/PD properties observed in the original region can be reproduced in the new region. In this context, for example, a statistical significance based on a particular endpoint can be also obtained from the bridging study conducted in new region if it had been observed in the original region. However, an equal or even larger sample size is required to reproduce a similar statistical significance for detection of treatment effect in the new region [3-6]. Therefore, these arguments indicate a fundamental conflict between the evaluation of similarity and the objective of minimizing duplication of clinical data in the ICH E5 guidance.

Consequently, Bayesian methods have been suggested to synthesize the data from both the bridging study and the original region to resolve this conflict [7,8]. However, some difficulties also arise using the Bayesian method. First, a medicine was approved in the original region due to its substantial evidence of efficacy and safety based on a sufficiently large sample size. The result of the bridging studies using empirical Bayes approach 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 completely opposite. In addition, the Bayesian method for evaluation of probability for error of decision-making on similarity is still needed to work out. This error probability is extremely crucial for the regulatory authority in the new region to approve a medicine in their jurisdiction.

IV. Summary

The ICH E5 guidance provides a rationale for assessment of ethnic factors in the acceptability of foreign data for regulatory strategies of minimizing duplication of clinical data and it also describes and requirement of bridging evidence for extrapolation of foreign clinical data to a new region. It, however, is too premature to develop statistical methods for regulatory implementation unless the scientific and clear criteria (a) for evaluation of sensitivity of medicines to ethnic factors, (b) for assessment of necessity of a bridging study, (c) for determination the nature and type of bridging studies, and (d) for assessment of similarity based on bridging evidence are defined in the ICH E5 guidance.

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Some Current Statistical Issues with Bridging

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The International Conference on Harmonisation (ICH) E5 guideline: "Ethnic Factors in the Acceptability of Foreign Clinical Data"1 introduces the concepts "bridging" and "bridging studies" and provides broad guidance on the process known as "bridging".ICH-E5 defines a bridging study as "a study performed in the new region to provide pharmaco-dynamic or clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data to the population in the new region". Simply put, the bridging process involves the extrapolation of clinical data generated from a foreign region (e.g. the West) to a new region (e.g. Japan) in order to obtain regulatory approval in the new region. Usually, the results of clinical trials conducted in the foreign region are known prior to conducting any clinical trials in the new region. The purpose of the bridging study is to generate enough data in the new region to demonstrate that extrapolation, or bridging, to the foreign region is possible. This will involve demonstrating that any differences in ethnic factors between the foreign and new regions have not altered the efficacy or safety of the drug in the new region. One of the advantages of the bridging process is that it negates the need for a separate clinical program in the new region and therefore avoids the need for unnecessary repetition of studies in the new region.

ICH-E5 states that if data generated from the bridging study shows that dose response, efficacy and safety in the new region are "similar" to the foreign region, the study may be readily interpreted as capable of bridging the foreign data. Although the ICH-E5 document is a major step forward, it does not contain guidance on the definition of "similarity". Subsequent to the issuance of ICH-E5, the then Ministry of Health and Welfare in Japan (now encompassed within the Japanese Ministry of Health, Labour and Welfare) produced a Q & A paper2, which states: 'it is impossible to suggest concrete standards to judge whether cited features of a drug are "similar" or "not greatly different" across populations'. It also mentions that: 'neither statistical "equivalence" nor strict identicalness is requisite'.

If this is the case, then, what are the criteria for successful bridging? Since bridging is a multi-faceted issue, not just a statistical one, there is no single, straightforward answer to this question. The final judgement necessarily depends on a number of important considerations: political, ethical, philosophical and clinical. Nevertheless, the application of appropriate statistical methods can make an important contribution to the bridging process, and the area of bridging is certainly rich with challenges for the statistician. This article discusses some of the statistical issues that arise with bridging, but is by no means a fully comprehensive account.

ICH-E5 recommends that a fixed dose, randomised dose response study should be the first choice for a bridging study. Information on dose response often plays an important part in extrapolability. It is not necessary to include an active control in the bridging study. ICH-E5 states that it is inappropriate to provide guidance on the sample sizing of the bridging study in that document, as this necessarily depends on the disease area and choice of endpoints. The simplest, and perhaps the most appropriate way to calculate the sample size for the bridging study, is on the proposed analysis of the bridging study itself (e.g. a trend test for dose response, or an expected difference from placebo). An alternative method of sample sizing for the bridging study is to base the calculation on a statistical analysis that will subsequently be used to demonstrate extrapolability of the foreign data. This approach, however, is likely to lead to a prohibitively large bridging study.

Once the bridging study has been designed and analysed, how do we then demonstrate extrapolability? Some statisticians have chosen to view the bridging problem in much the same way as they would view an equivalence or non-inferiority trial. Using this approach, the aim is to show that some appropriate measure of efficacy or safety in the new region (such as the treatment effect or slope of the dose response curve) and the same quantity in the foreign region, differ by no more than some positive amount, delta. Stating the problem in this way does not bring us any closer to a definition of similarity; it merely restates the same question in mathematical terms. The unanswered question: "what do we mean by similarity?" is replaced by another unanswered question: "what should we choose for delta?". Just as in equivalence and non-inferiority trials, the choice of delta would be a source of extensive debate, and would be different for different disease areas.

Another method of tackling the bridging problem is to fit a single statistical model to the combined data from the new and foreign regions, and test for the statistical significance of the treatment by region interaction (using appropriate measures of efficacy or safety as the outcome variables). This author considers that this approach is flawed in two ways. Firstly, although the detection of a treatment by region interaction means that the treatment effect is different between the two regions, it does not mean that the magnitude of the difference is of any clinical relevance. Secondly, failure to detect a treatment by region interaction, even in an adequately sized analysis, does not mean that there are no differences between the regions. As in all hypothesis tests, failure to reject the null hypothesis does not mean it has been proved to be true.

Rather than concentrating on the statistical significance of the treatment by region interaction term, an alternative approach would be to explore the nature and magnitude of this interaction using more informal methods, such as simple plots of the data, by region, with confidence intervals. Alternatively, or in addition to this, the treatment by region interaction term could still be fitted in a statistical model, but used to generate separate dose response slopes for different regions from the

same model. The standard errors for the estimated slopes can also be generated from the statistical model, and used to calculate confidence limits for the slopes. Covariates that may affect the estimates of the slopes may also be included in the statistical model. The assessment of similarity is then made from a visual inspection of the slopes. This judgement is made from a clinical point of view, but appropriate statistical methods have been used to (a) estimate the slopes of the dose response curves for each region, (b) provide appropriate measures of the variability in the estimates of the slopes, and (c) adjust the estimates of the slopes for any important covariates.

One popular approach to bridging between regions is to compare the results of a single bridging study in the new region with a single study of the same design from the foreign region. Usually, however, there is more than one study to choose from in the foreign region, and many of these studies could potentially contribute to the bridging analysis. One drawback of the "one-to-one" approach is that it can be difficult to provide a convincing justification for the choice of study from the foreign region if that choice is made after the results of the bridging study in the new region are known. One can easily be accused of choosing the foreign study with results that are "most similar" to the results from the bridging study in the new region. It may be preferable to identify which study from the foreign region will be used for bridging prior to knowing the results from the bridging study in the new region. But this may be a very difficult choice to make.

An alternative approach is to identify a set of studies in the foreign region that is representative of the overall clinical experience in the foreign region. That is, the studies should have a common set of endpoints, common design aspects, and include subjects from broadly the same population. The observed mean values of measured outcomes, or response rates, when calculated for the same endpoint will vary from study to study due to natural variation. This should not cause an issue for bridging, as the "similarity" of the results from the bridging study would then be viewed in the context of the variability already seen between studies in the foreign region. The study-to study variation could be modelled appropriately by fitting a study term as a random effect in a statistical model. There is also potential for the data from the foreign region and the data from the new region to be incorporated into a Bayesian model.

It is likely that at some point in the near future, bridging will be superseded by the emergence of global clinical trials (i.e. single trials that simultaneously recruit subjects from the United States, Europe, Japan and other countries). This author believes that these multi-region trials present much the same statistical issues (and controversies) as we currently encounter with multi-centre trials. We should approach the analysis of multi-region trials in much the same way as we currently approach multi-centre trials. Conventional wisdom from multi-centre trials would suggest that we should power a multi-region study to show an overall treatment effect across the regions and then explore the presence of heterogeneity of the treatment effects between the different regions. Once again, a treatment by region interaction test may not be the best way to explore these differences, but appropriate plots and summary statistics (with associated measures of variability) may be more useful and informative. The treatment effect used in any sample size calculation would be the treatment effect we expect to see in the study as a whole, and the by-region results would be examined to see if there are any departures from the overall finding.

There may be a tendency, however, for some regulatory authorities to request a subgroup analysis in their region alone. This then leads to special consideration of the proportion of subjects that must be recruited from a specific region in the study, so that meaningful subgroup analyses can be conducted in that region. If subgroup analyses are to be carried out, the type I error rate should be appropriately controlled, otherwise statistical significance could be seen in one of the regions just by chance. The statistical challenges involved in designing and analysing global clinical trials, which meet the requirements of different regulatory authorities throughout the world, are likely to remain with us for many years to come.

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Bridging clinical studies: many questions but few answers

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The concept of bridging studies was introduced in the ICH E5 document to facilitate the registration of pharmaceutical products among ICH regions. Clearly given in the document, a bridging study is defined as a study performed in the new region to provide pharmacodynamic or clinical data on efficacy, safety, dosage, and dose regimen in the new region that will allow extrapolation of the foreign clinical data package to the population in the new region. The similar concept can be stipulated in other contexts, such as, what data are needed to approve a drug for use in pediatrics given that the drug has been used for adult patients.

The first gigantic step is to decide whether a bridging clinical trial is needed for registration of a pharmaceutical product in a new region. The decision will involve a lot of knowledge, such as, the relationship between the pharmacodynamic response and the clinical outcome, inter-relations between these responses and covariables (e.g., ethnic factor, drug administration, medical practice) that are suspected to have influence on drug effect. The problem of surrogate markers needs to be of concern here and generally cannot be trivialized. On the other hand, if a drug has been approved to save lives in some disease patients in the foreign region, then how much of additional data are needed for the same indication to be granted in the new region? Extremely careful deliberation is very much needed because it has tremendous public health implication in the new region, knowing that direct explanatory power of pharmacodynamic data is limited.

When a bridging clinical trial is required, the expectation of little difference in drug effect between the new region and the foreign region is undoubtedly challenged. It is, however, not clear what the objectives of the bridging clinical study are. At the minimum, the bridging clinical study must conclude that a dose or dosage regimen of the drug chosen to be marketed in the new region is effective (i.e., beats placebo) and safe. Another objective is, as many argue, to show that this dose has similar therapeutic effectiveness as the dose approved for marketing in the foreign region. However, it is not clear why the latter objective is relevant for registration. This subject has already been discussed in literature, such as, Shao and Chow (2002), Liu, Hsueh and Chen (2001), Liu (2002), Ware (2001).

The bridging clinical trial has sample size limitation. The ICH E5 document describes the regulatory strategies that minimize duplication of clinical data in facilitating acceptance of foreign clinical data in the new region. To explore the feasibility of a bridging clinical trial, let d_2 be the dose to be marketed in the new region and d1 the approved dose in the foreign region,

where d_2 may or may not be the same as d1. Let θ_i be the corresponding mean effect (i =1,2). The foreign region has established the effect θ_1 with the estimate t1 and relevant 1-sided p-value $p1 < 0.025$. To test the efficacy of d_2 in the new region, the distribution of the p-value p_2 associated with θ_2 based on Hung et al (1997) is $\Pr\{ P2 \le p_2 \mid \theta_2 = \lambda\theta_1 \} = \Phi(-\Phi^{-1}(1-p_2) + M^{1/2}\lambda\theta_1)$, where Φ is the distribution of the standard normal distribution, M is the sample size of the new region, and λ is a constant. Assuming equal variability of the response between the regions, given t_1, the sample size M required for detecting $\theta_2 = \lambda t_1$ at significance level (and power 1-β is

$$M = N(\{\Phi^{-1}(1-\alpha)+\Phi^{-1}(1-\beta)\}/\{\lambda\Phi^{-1}(1-p_1)\})^2 .$$

Thus, for $\alpha = 0.025$ and $\beta = 0.20$, if $p_1 = 0.025$, then M will be 2.04N for detecting $\theta_2 = t_1$. If $p_1 = 0.001$, then M will be 0.82N. If (s have variability, then the sample size M will be even more demanding. Shao and Chow (2002) made similar arguments. In the context of showing similarity in drug effect between the two regions, it can easily be imagined that the sample size will need to be much greater (Liu, Hsueh and Chen (2001), Liu (2002)). Recognition of the sample size limitation of the bridging clinical study prompts several intriguing ideas for designing a bridging clinical trial. Examples are: Chow (2001) created a sensitivity index to determine the chance of reproducibility and generalizability based on the observed clinical data for determining when a bridging clinical trial with a certain sample size can be recommended, Shih (2001) stipulated the concept of showing 'consistency' by use of the predictive probability as a measure of the plausibility of the results of the new region given the known results of the foreign data, and Wang and Kung (2001) considered raising alpha error to exchange for sample size feasibility.

We should be reminded of the fact that in designing a bridging clinical trial there has been substantial to rich experiences with the drug from the foreign data. Perhaps the dose response data are not sufficient for extrapolation. But at least, there is plenty of experience with the marketed dose of the drug. Can the foreign data help to refine the clinical and statistical hypothesis for bridging clinical trial? For instance, when testing hypothesis of similarity, can we consider only the type I error rate within the new region. That is, the uncertainty in the estimate of the drug effect from the foreign region is only used for the purpose of designing the bridging study, not incorporated in the calculation of type I error for the new region. Another question is, should one-sided hypothesis be sufficient? Flexibility must be kept in mind in each application at hand.

In this era, drug development has become global. Thus, at the planning stage of drug development, the strategy of global multi-national clinical trial is appealing. Each region becomes a specific subgroup. Internal validity can be achieved. This strategy will demand consistency in clinical trial standards and regulatory standards among the regions. However, if regional differences in drug effect are suspected, then the percent representation of each region will become a contentious issue. Nonetheless, the global average of θ's will better reflect the drug effect over the multiple regions. Can the global clinical trial strategy solve the problem of bridging clinical trial? It is not likely. We have long experienced the difficulty in interpretation of subgroup results when the subgroup analysis shows apparent heterogeneity among subgroups. In fact, the problem

of the bridging clinical trial strategy can be in some sense just the manifestation of the problem of the subgroup analysis.

How much evidence together with how much belief will continue to drive interpretation of subgroup analysis and design of bridging clinical study. The spirit behind the two strategies is the same; that is, regional differences in drug effect are not expected unless proven otherwise. If the initial expectation is that the drug effect differs among regions, then the strategy may have been very different to give an ample opportunity to reject the expectation. As the human genome is complete, the study of genetic makeup in various ethnic groups may help to design a more sensitive clinical study. The framework of statistical inference may also have to evolve to provide statistical power for uncovering the mystery.

Acknowledgment

The authors are grateful to Drs. Jen-Pei Liu and Mey Wang for many stimulating discussions on this topic.

Disclaimer

The views presented in this article are solely those of the authors and do not represent those of the U.S. Food and Drug Administration.

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Some Upcoming Statistical Meetings

Third International Conference on Multiple Comparisons Procedures
August 04–07, 2002, Bethesda, Maryland, USA

Beyond the Formula Statistics Conference
August 08–09, Rochester, New York, USA

2002 Joint Statistical Meetings
August 11–15, 2002, New York, USA

The 4th Survey Research Methodology and Its Applications Conference.
August 29–30, 2002, Academia Sinica, Taipei, Taiwan.

Statistical Concepts for Non-Statisticians
September 09–10, 2002, San Diego, California, USA

Symposium on Biomedical Technology Development (visit our website for details)
September 28–29, 2002, Rockville, MD, USA

Applied Statistics Conference at NC State
October 30–01, 2002, Raleigh, North Carolina, USA

The Second Annual Emerging Information Technology Conference — Nanotechnology, MEMS, Systems on Chip, and Bioinformatics Workshops
November 01–02, 2002, University of Princeton, Princeton, New Jersey, USA

BAMMCONF: Bayesian Applications and Methods in Marketing Conference
November 13–16, 2002, Columbus, Ohio, USA

Eleventh Annual Meeting of the International Genetic Epidemiology Society
November 15–16, 2002, New Orleans, Lousiana, USA

10th Merck-Temple Conference
November 22–22, 2002, Philadelphia, Pennsylvania, USA

International Conf. on Applied Statistics, Actuarial Science, Financial Mathematics
December 17–19, 2002, Hong Kong, International China

ICSA 2003 Applied Statistics Symposium (visit our website for details)
June 22–24, 2003, University of San Diego, San Diego, California, USA

********** See You at Big Apple **********

INTERNATIONAL CHINESE STATISTICAL ASSOCIATION

Events at 2002 Joint Statistics Meeting at New York

Caucus of Women in Statistics (ICSA Cosponsored)
Time: 6:00 PM–7:30 PM, Sunday, August 11, 2002
Place: Mercury Rotunda at Hilton Hotel

Board of Directors Meeting
Time: 7:30 PM–10:30 PM. Sunday, August 11, 2002
Place: Liberty Suite 3 at Sheraton Hotel

Statistica Sinica Board of Directors Meeting
Time: 10:30 AM–12:00 PM, Tuesday, August 13, 2002
Place: Liberty Suite 5 at Sheraton Hotel

Statistica Sinica Invited Papers Session
Time: 8:30 AM–10:20 AM, Wednesday, August 14, 2002
Place: Royal Ballroom B at Sheraton Hotel

Membership Meeting
Time: 6:00 PM–7:30 PM, Wednesday, August 14, 2002
Place: Concourse B at Hilton Hotel

Year 2002 Banquet
Time: 7:30 PM, Wednesday, August 14, 2002
(Right after the Membership Meeting)
Place: The Peking Park Restaurant at 100 Park Ave., NY, NY 10017
Entrance at 40th Street, Between Park & Madison Ave.
After Banquet Entertainment: Karaoke (please volunteer!)
Cost: $30/person

Please register and pick up Banquet ticket at the ICSA Booth at JSM2002.
To help for head count, please register before Wednesday, August 14

Information and Banquet Registration:
Wei-Yann Tsai, wt5@biostat.columbia.edu, tel # 212-305-9408

ICSA 2003 APPLIED STATISTICS SYMPOSIUM

JUNE 22-24, 2003
San Diego, California
http://www.icsa.org

Theme: Statistics in Bio-tech Research and Computing Intensive Methodologies

DATE: June 22 to 24, 2003. Short courses on Sunday, June 22, and technical sessions on Monday, June 23 and Tuesday, June 24.

LOCATION: University of San Diego. For local attractions, please visit the hotel website http://www.sandiego.org/whattodo.asp

ACCOMMODATIONS: The room rates of lodging at University of San Diego range from $50.00/night /person without meal to approximate $100.00/night/person with meals.

CALL FOR PAPERS: The program committee invites you to submit statistical papers to be considered for presentation at the symposium. Abstracts are due March 31, 2003. Please submit abstracts to: Professor Gang Li, University of California at Los Angeles, email address: gangli@sunlab.ph.ucla.edu. The abstract should include the name, affiliation, mailing address, telephone number, fax number, and e-mail address of the author, and should not exceed 200 words. A template for the abstract can be downloaded from the ICSA website at http://www.icsa.org

ICSA STUDENT AWARDS AND TRAVEL FELLOWSHIPS: The deadline is February 28, 2003 (see a separate page in this issue for detailed information). For further questions, please contact Professor Kung Jong Lui, San Diego State University, kjl@rohan.sdsu.edu

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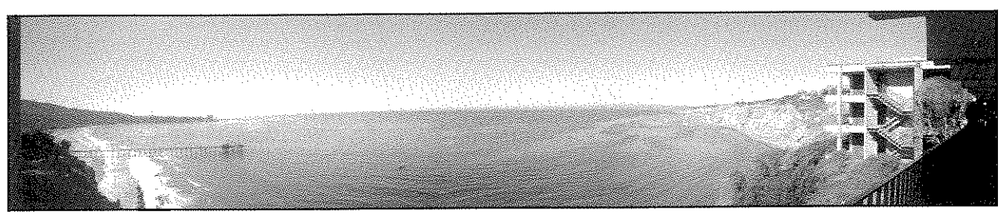
PRELIMINARY PROGRAM
ICSA 2003 APLLIED STATISTICS SYMPOSIUM

- **Keynote Speakers (June 23-24, 2003):**
  Bradley Efron, Professor of Statistics and Biostatistics, Stanford University, President-Elect, ASA.
  http://www-stat.stanford.edu/people/faculty/efron.html
  George Tiao, W. Allen Wallis Professor of Econometrics and Statistics, University of Chicago,
  http://gsb.uchicago.edu/fac/george.tiao

- **Plenary Sessions (June 23-24, 2003):**
  Recent developments in nonparametric inferences with applications to biomedical studies and financial modeling, by Janqing Fan
  PK-PD modeling in drug research and development, by Tze Leung Lai

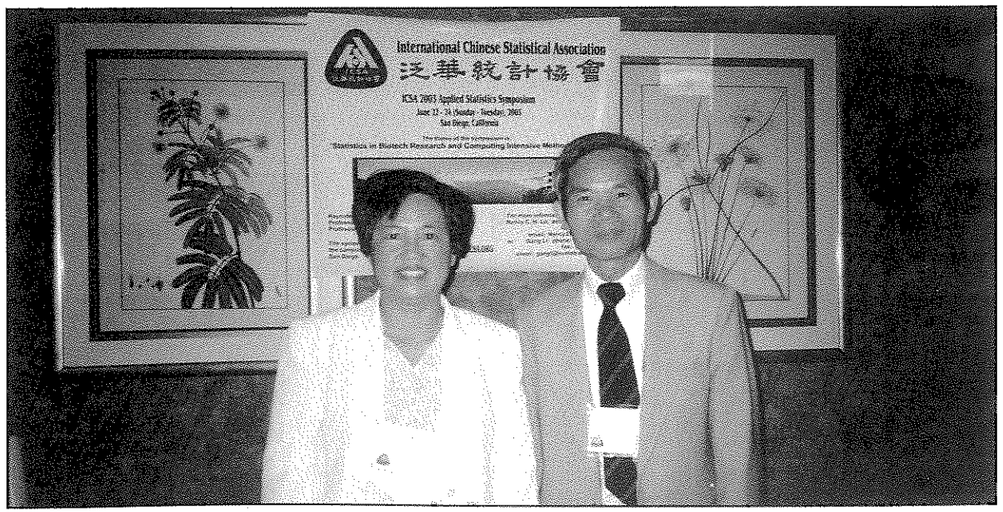
- **Banquet Speaker: Arlene S. Ash, Boston University. (Lucky Star Chinese Sea Food Restaurant.)**
- **Short Courses (Sunday, June 22, 2003):**

	Topic	Instructor
1	Practical Guidance of Generalized Linear Mixed Models	Charles E. McCulloch, University of California, San Francisco
2	Tutorial on Statistical Bioinformatics	Jun Liu, Harvard University
3	Cancer Trials for Practitioners - Experimental Design, Efficacy Analysis, and Economic Implications	Kao-Tai Tsai, Aventis Pharmaceuticals
4	Bootstrap Methods: A Guide for Practitioners	Michael R. Chernick, Novo Nordisk Pharmaceuticals
5	Active Controlled Clinical Trials	Yi Tsong and Sue-Jane Wang FDA
6	Robust Parameter Design for Product/Process Improvement	Jeff Wu, University of Michigan



Invited Sessions (June 23-24, 2003, not complete):

	Topic	Organizer
1	Statistical Applications in Business Research	Chih-Ling Tsai
2	Issues of Active Controlled Clinical	Trials Tsong Yi
3	Statistics in Risk Management	Jianqing Fan
4	Current Methodologies in Pharmaceutical Statistics	Kerry B. Hafner
5	Assessment of Measurement Agreement	Richard Runze Li
6	Recent Advances in Survival Analysis	Gang Li
7	Data Mining in Chemistry and Chinese Medicine	Kai-Tai Fang
8	New Development in Medical Diagnostic and Screening Tests	Andrew Xiaohua Zhou
9	Statistical Methods for AIDS Clinical Research	Hulin Wu
10	Design of Experiments	Ching-Shui Cheng
11	Design and Analysis of Dose Response Studies	Naitee Ting
12	Statistical Applications in Accounting, Economics and Finance	Ruey S. Tsay
13	Empirical Likelihood and Its Applications	Songxi Chen and Wei-Liem Loh
14	Computing Intensive Methodologies in Bayesian Statistics	Minghui Chen
15	Functional Data Analysis	Xiaoli Meng
16	New Development in Quality Improvements	Smiley W. Cheng
17	Statistical Methods for the Analysis of DNA and Tissue Microarray Data	Steve Horvath
18	Markov Chain Monte Carlo and Its Applications	Dongchu Sun
19	Aspects of Clinical Trials	Grace Yang
20	Bioengineering and Statistics	Nancy Lo
21	Intensive computing in genetic application	Frank Shen



Student Award Winners

From: Weichung Joe Shih
Chair of the student awards and travel fellowship committee

TO: ICSA President, Executive Director, and Symposium Program Chair

Five papers have been submitted for the 2002 ICSA Student Awards and Travel Fellowships program by the deadline of Feb 28, 2002. The Student Award Committee (W. J. Shih of Univ. of Medicine and Dentistry of New Jersey, Cun-Hui Zhang of Rutgers University and Zhiliang Yin of Columbia University) has selected the following three papers according to the program guidelines.

These students and paper titles are (by the order of ranking):

1. Zhengjun Zhang, University of North Carolina, Chapel Hill. "Modeling financial time series data as moving maxima processes". (With Richard L. Smith)

2. Jun M. Liu, University of Illinois at Chicago. "Modelling hourly electricity loads using a semi-parametric time series approach". (With Rong Chen and Lon-Mu Liu)

3. Yi-Chuan Zhao, Florida State University. "Goodness-of-fit test for proportional hazards assumption via empirical likelihood". (With Ian W. McKeague)

Each of the above three students will receive a certificate, $400, and tuition for the short courses of their choice at the Symposium.

Registration Form

Biomedical Technology Development

September 28~29, 2002
University of Maryland, Shady Grove Campus, Building I, Auditorium
9640 Gudelsky Drive, Rockville, MD 20856

Name	(Chinese) (English)
Organization	
Address	
Tel.	(O) (H)
Fax.	(O) (H)
E-mail	

	Before 9/10/02 (per person)	After Sept. 10 (per person)	Vegetarian (Yes or No)	Num. of person	Total
Registration fee (include 09/28 lunch)	$25	$30			
Banquet 09/28/02	$20	$20			
Total amount					

1. Please mail the registration form and a check payable to **"SCBA"** by 09/10/2002 (no cash, please) :
   SCBA, c/o Ms. Pat Oldewurtel
   Johns Hopkins Asthma and Allergy Center, Room #1A-62
   5501 Hopkins Bayview Circle, Baltimore, MD 21224
   Tel: 410-550-2001 Fax: 410-550-2527

2. Registration fee includes program book, lunch (9/28), coffee, soft drink.

3. Please call (8:30~17:00):
   Shau-Ku Huang (410-550-2006); Sue-Jane Wang (301-983-3591)
   Cathy Wu (202-687-2121); Shiew-Mei Huang (301-827-7688)
   Jih Shao (202-895-1931).

Symposium on Biomedical Technology Development

September 28-29, 2002

University System of Maryland, the Shady Grove Center

9640 Gudelsky Drive, Building I-134, Auditorium 305

Rockville, MD 20850

會議行程 (Program)

Day 1	September 28 (Saturday)
Plenary session	
08:30 – 08:35	Opening Remarks Dr. Yaw-Nan Chen 陳燿南, TECRO-Science Division - to be confirmed
08:35 – 09:40	Keynote Speech (Dr. Yaw-Nan Chen to confirm)
09:40 – 10:00	Morning Break
Session 1	Emerging Biotechnology - Vaccine Development Don Chen 陳東勝, Ph.D., SynAm Keith Chan 陳桂恆, Ph.D., GloboMax
10:00 - 12:00	• Vaccine Shau-Ku Huang黃嘯谷, Ph.D. Johns Hopkins • Vaccine Industry- OEM or OPM for innovation Wenlii Lin 林文理, Ph.D. ADImmune • The Need of Vaccine Development in Taiwan Shiing-Jer Twu 涂醒哲M.D., Ph.D., Director General, CDC, Taiwan • Panel Discussion (Clinical and Regulatory) Shousun Sze, 陳孝生 Ph.D. NICHD/NIH Kimi Feng-Ying C. Lin, 邱鳳英 M.D. NICHD?NIH Chi-Jen Lee, 李啓仁 D.Sc. CBER/FDA.
12:00 noon-1:00 pm	Lunch (cafeteria)
Session 2:	Current Biotech Investment in Taiwan and Europe Chuang C. Mike Chiueh 闕壯卿, Ph.D., NIH Leon Tseng 鄭良福, Ph.D., Medical College, Wisconsin

13:00 - 15:00	• US Patent developed by Academia: antisepetic Shock or iNOS Suppresser M.J. Su 蘇銘嘉,Ph.D., Pharmacology Institute, National Taiwan University, Medical School • US Patent developed by Industry: Anti-enterovirus Agents from Algae C. Chun Chiueh 闕壯群, C.E.O, FarEast Algae • Clinical Trials: Conjugated Blood Clot Busters P. -W. Hong 洪博文, M.D. / S.S. Yang 楊適旭, GlobalGene • Emerging European Biotech Company: From Bench-Top Idea--Patents--Clinical Trials of New NO Drugs Piero Del Soldato, Ph.D./ Jean-Luc Burgaud, Ph.D, Nicox SA
15:00 - 15:30	Afternoon Break
Session 3	Biochip Technology and Data Mining Sue-Jane Wang 王淑貞, Ph.D., CDER/FDA Cathy Wu 吳慧華, Ph.D., Georgetown University
15:30 - 17:30	• "Seriation algorithms for identifying smooth temporal pattern and global clustering structure in cDNA gene expression data" Chun-Houh Chen 陳君厚, Ph.D., Institute of Statistical Science, Academia Sinica, Taipei, Taiwan • "Current status of biochip technology development, where is it headed, and its commercialization potential" Chung-Cheng Liu 留忠正, Ph.D., Industrial Technology Research Institute, Hsin Chu, Taiwan • "Bioinformatics and Functional Genomics/Proteomics" Cathy H. Wu 吳慧華, Ph.D., Georgetown University
19:00 – 22:00	Dinner Banquet (New Fortune restaurant 新財神, Gaithersburg, MD)
	Dinner speaker World renowned forensic criminal scientist--- Henry Lee 李昌鈺博士, Ph.D.
Day 2	**September 29 (Sunday), 2002**
Session 4:	Pharmacogenetics, pharmacogenomics, and biomarkers: When is personalized medicine possible? Shiew-Mei Huang 李秀美, Ph.D., CDER/FDA Shau-Ku Huang 黃嘯谷, Ph.D., Johns Hopkins University

08:30 - 10:30	• Pharmacogenomics in Asia-VitaGenomics' experience Ellson Chen 陳奕雄, Ph.D., VitaGenomics, Taiwan • Integration of Pharmacogenomics into Health Care Michael Shi 石明 M.D., Ph.D., FACB, Sequenom, Inc., San Diego
10:30 – 11:00	Morning Break
Session 5:	Taiwan Biopharm Lessons from the Past and Hopes for the Future Shaw Chen 陳紹琛, MD, PhD, CDER/FDA Keith Chan陳桂恆, Ph.D. Don Chen 陳東勝, Ph.D.
11:00 –12:00	• Biopharmaceuticals: Challenge and Opportunity for Taiwan Darrel Liu 劉德勇, Ph.D., (affiliation) • (Presentation title?) Chi-Ming, Liang 梁啓銘, Ph.D., Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan, Title TBA • Lessons from the Past and Hopes for the Future - Taiwan and US CMO Perspective Michael Huang 黃一旭, Ph.D., DVM, Mycenax Inc., Taiwan
12:00	Closing Remarks Dr. Yaw-NanChen 陳燿南, TECRO-tentative

For additional information of this program, please contact the organizing committee.

- Keith Chan 陳桂恆: (O) 301-340-7500; (fax) 301-340-7833; chank@globomax.com
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- Jih Shao 邵驥: (O) 202-895-1931;(fax)202-895-1939 de@tecrosd.org
- Sue-Jane Wang 王淑貞: (O) 301-827-3089; wangs@cder.fda.gov
- Cathy Wu 吳慧華: (O)202-687-2121 wuc@nbrf.georgetown.edu

If I Could Do It All Over Again

T. Timothy Chen
Southwestern Baptist Theological Seminary

Why do I give advice?

I still remember the day when I arrived at Chicago O'Hare airport on September 15, 1967. After checking into my room at International House, tears came down my eyes. My first time alone, so far away from home with no friends near by, I experienced a feeling of helplessness. I tried to seek advice and help from many people who had come to the US before me. Now almost thirty-five years later, with a wife of 33 years and two adult sons, a good statistical career, I feel totally at home in this adopted homeland.

This issue is the last one under the editorial leadership of Dr. Sue-Jane Wang. She has been a faithful supporter of the Washington DC seminar group that I started in 1990, and she took over the responsibility as the editor-in-chief of ICSA Bulletin under my presidency of ICSA in 1999. I was involved in the ICSA business as a board-director since 1991 for three 3-year terms and attended all the board meetings. During my term of presidency, ICSA started the first Student Awards and Travel Fellowship for the ICSA Applied Statistics Symposium, agreed to move the Symposium meeting site to other places away from the East Coast, and for the first time offered a reduced fee for statisticians residing in developing countries. I have enjoyed my service to the ICSA, including establishing a journal donation service for the libraries in China. .

I organized several times mentoring sessions at the ICSA meetings. I also gave a mentoring talk during the ICSA Applied Statistics Symposium two years ago. When Dr. Sue-Jane Wang asked me to summarize my talk given there, I began to reflect on these 35 passing years again. What of my experience could be beneficial to the new generation of students from China? How could I help them to adjust to this new land?

How important are having good mentors?

I had good mentors during my first career in the past 35 years. Professor Stephen Fienberg, my dissertation advisor, was very helpful in guiding me to work on the problem about missing incomplete data in categorical data. Dr. Edmund Gehan, my mentor at M. D. Anderson Cancer Center for five years, helped me understand the issues in cancer research and statistics. Dr. Richard Simon, my boss at National Cancer Institute for nine years, worked together on methodology for cancer clinical trials, showed me the responsibility of a researcher at a governmental granting agency, and provided me a good example of success through hard work. I regard myself as extremely fortunate to have them as my mentors; from them and others I have learned a great deal.

Nonetheless, if I could do it all over again, I would try to learn more and get more help from my mentors. Having good mentors is one of the most important factors for a successful career. This fact is confirmed repeatedly in different studies of the sociology of science. To have a good mentor, one needs to have a learning attitude and an ability to work hard. Besides actual people as mentors, one can also learn a lot from books. *Advice to a Young Scientist* (Harper and Row, 1979), writ-

ten by Nobel Laureate P. B. Medawar, was acclaimed to be a very good and helpful book. *How to Get a Ph.D.* (Open University Press, 3rd edition, 2000), by Estelle M. Phillips and DS Pugh, gives tips about how to do research and how to manage your advisor. *Getting What You Came For: The Smart Student's Guide to Earning a Master's or a Ph.D.* (Noonday Press, 1997) written by Robert L. Peters, and *The Ph.D. Process: A Student's Guide to Graduate School in the Sciences* (Oxford Univ Press, 1998) by Dale F. Bloom, JD Karp, and N. Cohen are widely read and consulted.

What are the American values?

When my sons were growing up, I tried to help them to develop their potentials fully. I encouraged them to try out everything according to their interests. They were not brilliant, but they were diligent, with a sense of purpose and the power to concentrate. They enjoyed experiments either with hand or in mind. They cultivated a love for discovery and originality. They were reminded to persevere and not be cast down by adversity. They were born and grew up in America, so they appreciate American idea of freedom and believe in the inherent worth of every man and woman. We as parents acted as custodians and facilitators then, and now as friends and encouragers.

My wife and I grew up in Taiwan and came to the US for graduate study. We have lived more years here than in Taiwan or China. We come to realize that there are important characters and values, which shaped the American society. During the seventeenth century, immigrants from Europe settled in the New World for the opportunity of a better life and religious freedom. The US was and still is a country of immigrants. American people cherish optimistic and can-do spirit, individualism, entrepreneurism, and pragmatism. They appreciate self-help, self-improvement, and self-education, and the reward is usually appropriated by competence and merit. Since the freedom of speech is considered the fundamental liberty, the ability and boldness to communicate are highly valued. The backbone of all these manifestations is found in the religion of Judeo-Christian faith. Liberty, equality, and charity are considered as basic moral values derived from the religious faith. Therefore, people contribute their volunteering effort and form association to work for the common good.

How to be a good researcher?

To enjoy our lives in the America, besides appreciating and adopting the American values, we have to do a good job in our profession as statisticians. Individually we need to manage our own time wisely. Everyone is given equally the same twenty-four-hours day; successful people don't waste their time. We need to be diligent in our reading and learning, not only in statistics, but also in the general culture. We also need to project good appearance, maintain certain assertiveness, and seek visibility and influence. Collaboration and networking are essential, so it is important to be able to work with others in a congenial spirit. Contributing our time and effort to review and edit journals and to organize programs for the professional societies, such as ICSA and ASA are our responsibilities and privileges.

If one chooses an academic and research career, there are some useful guides for the whole scientific career. *A Chicago Guide to Your Academic Career: A Portable Mentor for Scholars from Graduate School Through Tenure* (Univ of Chicago Press, 2001), by John A. Goldsmith, J. Komlos, and PS Gold, and *A Ph.D. is not Enough: A Guide to Survival in Science* (Perseus Publication, 1994) by Peter J. Feibelman are well recommended. *Tomorrow's Professor: Preparing for Academic Careers in Science and Engineering* (IEEE, 1997), by Richard M. Reis, is written especially for teachers in science, so is applicable to statistics.

How to be a good communicator?

The ability to communicate by writing and speaking is essential for a successful career if one is not a genius. *How to Write and Publish a Scientific Paper* (Oryx Press, 5th edition, 1998) written by RA Day is a standard reference. *Getting it Published: A Guide for Scholars and Any One Else Serious about Serious Books* (Univ of Chicago Press, 2001), by William Germano, is a recent entry. *Communicating in Science: Writing a Scientific Paper and Speaking at Scientific Meetings* (Cambridge Univ Press, 2nd edition, 1993), by V. Booth, covers both areas of communication. *Dazzle 'em with Style: The Art of Oral Scientific Presentation* (WH Freeman & Co, 1994), by RRH Anholt, is a good book. Smart Speaking (Plume, 1992), by L. Schloff and M. Yudkin, is good for oral communication in general.

Related to the communication is the ability to teach. For those who elect the academic career, the following two books will be useful for improving teaching skills. *Classroom Assessment Techniques: A Handbook for College Teachers* (Josey Bass, 2nd edition, 1994), by KP Cross and TA Angelo, is a good resource in the series for teachers. *McKeachie's Teaching Tips: Strategies, Research, and Theory for College and University Teachers* (DC Heath & Co, 11th edition, 2001), by WJ McKeachie and G Gibbs, is a standard reference.

The ability to write grant proposal is also critical for a career in academy. *Writing Successful Science Proposals* (Yale Univ Press, 2000), written by Andrew J. Friedland and Carol L. Folt, and *Proposals that Work: A Guide for Planning Dissertations and Grant Proposals* (Sage Publications, 4th edition, 2000), by LF Locke, WW Spirduso, and SJ Silverman, should prove to be helpful.

The following two books are helpful for finding a job after finishing school. *What Color is Your Parachute? A Practical Manual for Job Hunters and Career Changers* (Ten Speed Press, 32nd edition, 2001), by R. N. Bolles, is for all kinds of careers; T*he Academic Job Search Handbook* (Univ of Philadelphia Press, 2nd edition, 1996), by MM Heiberger and JM Vick, is especially geared to job searching in the academy.

How to conclude a life?

Above is a summary and a revision of the talk I gave at 2000 ICSA Applied Statistics Symposium. After working thirty years as a full-time statistician in academy, industry, and government, my experience could be useful to the new generation of Chinese students. I do not claim that I have learned all I could or I have practiced all I learned. In fact, I just started my second career as a Christian theologian beginning with a graduate study toward a Ph.D. degree. I now have a second chance to practice what I said here.

We are reading more and more about elderly Americans going back to college to learn new things and enjoy their golden years. Many colleges have special programs catered to the senior adults. Even many senior communities are sprung up near college campuses. Life long learning is definitely a possibility and becoming a reality. We could really have two productive careers. It all depends on whether we are willing to learn and try new things. If we do, we can enjoy our lives to the fullest as endowed by our Maker.

What do I know about the pharmaceutical industry?

Chiayu Lin, MPhil
Institute of Statistical Science, Academia Sinica
Taipei, Taiwan

Though the pharmaceutical industry has been in history for decades, and it is one of the top businesses in the U.S. recently, I got to know deeply about this industry as a freshman about 3 months ago. Here I'd like to share what I know and what I feel about the pharmaceutical industry from the standpoint of being a biostatistician.

The scientists spent plenty of time exploring a compound that may have potentially therapeutic effect to improve the quality of human lives by the means of shortening the duration of disease/disorder syndromes and of prolonging the human lifetimes.

The process that a compound has to go trough in order to be acceptable safe for human usage is multi-stage and multi-disciplinary, and that includes the manufacture and storage of the substances, pre-clinic tests of toxicity, animal studies of allowance safe doses, human clinical trials of efficacy and safety, and post-market test of drug comparisons and future safety concerns. To ensure the strength, purity, effectiveness, safety of the substance, several authorities set up the corresponding specifications and regularities at each stage. It is multidisciplinary because it takes scientists, medical doctors, and biostatisticians to tradeoff among many standards, which even involves in the ethnics and finance.

Nothing is 100% for sure to have no harm to the human bodies, yet the effort input to the pharmaceutical industry is a tradeoff between benefit and risks. Besides, there exist individual differences. However, conclusions made are for the majority. Biostatisticians would generally say that there is an allowance of 5%, say, of error in concluding that the drug is effect while it is indeed not, the false positive rate, and that 20%, say, of chance to conclude that the drug is not effect while it is indeed to be, the false negative rate. Especially, since the process to have a drug on market takes multiple stages, it is desirable to set up standards at each stage to ensure that final drug has the potency, purity, effectiveness and safety as it is claimed.

From the viewpoint of being a biostatistician, it is a shame to say that we love to make conclusions for the majorities while only based on small sample evidences, which are generally of little confidence. However, it could be said that it would be improved if there were more studies conducted. Nevertheless, it is general infeasible due to a couple of reasons. Firstly, it is time-consuming. The average time period for a compound to be classified as a drug on the market is about 12-15 years, and the average life time of human beings is around 65-75 years. Additional, not all but small percentage of substances explored is eligible to be on the market. Secondly, it is a money-driven business. A single study run during the potential compound and/or the new drug investigation takes only a small percentage of the total cost. Besides, for the sakes of economic balances and the timer of the disease, it is preferred to have drugs on market as soon as possible.

Therefore, one solution in this industry is to pick up the minimum benefit and the maximum cost/risk while conditioning on the achievement of baseline benefit. The maximum tolerable dose level is picked up for the sakes of safety, and the minimum relieve of disease symptoms is depicted to evaluate the population efficacy of the drug. One concern of this viewpoint is that individuals make decisions of whether to take the drug based on individual benefit and risk. Even if for the viewpoint of social health welfare, it seems more likely that some patients would not be properly cared due to the high cost of treatment, while comparing the benefit-risk ratio among diseases.

While the economic issue belongs to pharmaeconomists, what a biostatistician could do about it? One way is to improve the computation of the minimum sample size of a study in order to detect the clinical effectiveness with the maximum power, as well as the study designs. The other way is to improve the specification at each drug-development stage to ensure the effectiveness of the drug as it is claimed. It is no doubt that the design plays the most important role in a study. The selection of it depends on the hypothesis of interest, the sample size and the budget, as well as the efficiency and optimality of the test statistics.

At the end of a study, the statistical conclusion about a hypothesis testing is carried out, thereafter; of concern would be whether to schedule the following study or whether to market the drug. And the primary concern would fall in the category of being unable to reject the null hypothesis. While it happens it is not said that the null hypothesis is accepted, yet data does not provide enough evidence to reject it. If the data is representative, then the failure to reject the null hypothesis means that the probability of making the wrong conclusion that the drug is effective while the it is not is over 5%, say, and the probability of making the wrong conclusion that the drug is not effective while it is is less than 20%, say. It sounds like that the potential drug has effectiveness with higher possibilities than it has no. At this moment, while the re-enrollment of patients in this study is not possible, how certain could it be to draw conclusions that the drug is ineffective and it should be abandoned. What value would p-value of an efficacy test be such that no further investigation would be necessary? It may be a good idea to suggest that when $\alpha=\beta$. Then when does $\alpha=\beta$?

Two examples are considered.

(1) Normal distributed data
Assume μ_0 and μ_1 are two independent sample means, and of interest is to test

$H_o: \mu_0=\mu_1$ vs. $H_A: \mu_1=\mu_0+\delta$,
then the type I error

$$\alpha= p(T > (t_{(\beta, n_1+n_2-2)} + \delta)/\sqrt{1+\mathrm{var}(\bar{x}_1-\bar{x}_0)}),$$
and

$$t_{(\beta, n_1+n_2-2)}=-\delta/(1+\sqrt{\mathrm{var}(\bar{x}_1-\bar{x}_0)}),$$
thus, β can be solved from the table of t distribution.

(2) Binary data
Assume p_0 and p_1 are two independent sample proportions, and of interest is to test

$H_o: P_0=P_1$ vs. $H_A: P_1=P_0+\delta$
The test is to reject

$$\hat{P}_1-\hat{P}_0 > Z_{1-\alpha}\sqrt{\bar{P}(1-\bar{P})/(n_1+n_2)},$$
then

$$Z_{1-\alpha}= \delta/\sqrt{\bar{P}(1-\bar{P})/(n_1+n_2)} - 1,$$
thus, α can be located by standard normal Z distribution.

In both cases, it is claimed that no further investigation of the compound would be conducted if the p-value of the current trial is larger than the α or β value computed.

Another solution is to wait for more the same studies being conducted and to com-

bine small studies to make the conclusion. And that raises the importance of meta-analysis.

While there exists only study population difference among phase I-IV clinical trials, whether it is a good idea to treat the result of previous phase of clinical trials as prior information to test the efficacy of the current trial? This answer is positive and has been looked into by several articles. On the other hand, the bridging study claims to waive phase I and II studies while the new drug investigation is completed and passed at one country and is conducting at another one and several criteria have been met. The use of it is controversial, primarily due to the representativeness of the new population by the original population.

The lengthy scientific process for a compound to provide promising effectiveness could be shortened by the study of bioavailability, which compares the therapeutic equivalence by testing the rate or the extent to which the drug becomes available at the site of the body between/among different formulations of a drug. This equivalence test is different from the conventional equality test by a selection of a clinically meaningful difference, and the null hypothesis is rejected if the absolute value of the test statistics minus some meaning difference is small enough, i.e. of interest is to test

$$H_0=|\mu_1-\mu_2|>\delta \text{ vs. } H_A=|\mu_1-\mu_2|<\delta.$$

The pharmacokinetic model of the drug absorption, distribution, metabolism, and elimination is assumed. This is the main factor that causes individual difference in the response to drugs. A preferred design is to treat each individual as a block to receive all/partial formulations of interest, and to separate treatment periods by an enough long period of time to have previous drug effect washed out. This is the so-called crossover design. A 2-by-2 crossover design estimate the drug effect by taking the intra-subject effect while a higher order crossover design is useful to consider the inter-subject effect. Besides carryover effect, it is also of concern that whether the sample size of sequences is equal.

While the drug product is ready to be on the market, how long its potency could be of certain within 90%, say, of the label claimed. Stability study estimates the rate of degradation of the drug potency, say β_1, and picks up the time that is the intersection of the 95% lower bound of the degradation curve with the horizontal line of 90% label claimed to be the expiration date. Mathematically, it is written as follows.

The working-Hotelling $100x(1-\alpha)\%$ confidence lower bound for $Y=\beta_0+\beta_1 X$ is a hyperbola

$$L=\beta_0+\beta_1 X-\sqrt{2F(1-\alpha;2,n-2)}\times\sqrt{var(Y)},$$

where $var(Y)=\sqrt{MSE(1/n+(x-\bar{x})^2/\Sigma(x-\bar{x})^2)}$

and $MSE=\Sigma(Y-\beta_0+\beta_1 X)^2/(n-2)$.

The expiration date is the solution of X which satisfies the above equation while L is replaced by 90%. In other words, with mass production, if the drug product is stored properly, then the expiration date is the date on which we have 95% of confidence to conclude that the drug potency is 90% of the label claimed. This is critical, since relative humidity and weather temperature vary across regions and countries.

This article is one viewpoint of the author's as a freshman in the pharmaceutical industry. Many important issues in the pharmaceutical industry may not have been viewed by the author yet while many issues pointed out in this article may have been looked into by many other articles. The author is thankful for Dr. Shein-Chung Chow for his consultation and recommendation of submitting to the ICSA bulletin.

STATISTICS' DELIGHT

統計趣聞

統計謎語

● 如果統計是從有限的資料、線索尋找答案的一門學問，則謎語也可以看做是統計問題。

根據以下的提示，射一統計相關

1. 胎記。
2. 生不如死。
3. 此山是我開，此樹是我栽。
   欲由此處過，留下買路財。
4. 織布。
5. 前有猛虎，後遇豺狼。
6. 春花秋月何時了，
   往事知多少。
7. 遇見尼姑，逢賭必輸。
8. 魏蜀吳, 三分天下。

答案

1.Biomarker
2.Quality of Life
3.FDA & User Fee
4.Cross-over Process
5.Competing Risks
6.Short Memory Time Series
7.Causality Analysis
8.Market Segmentation

Trivia

☺ ☺ ☺

The eyes of some birds weigh more than their brains

Mozart wrote the nursery rhyme tune "Twinkle, Twinkle, Little Star" at the age of five

A duck has three eyelids. That way he can open it just a quack!

The act of snapping your fingers is called "fillip"

☺ ☺ ☺

From Meredith G. Warshaw

From the Warshaw's Field Guide to Atypical Statistics*

❤ Box plot: a cabal planning to hide surreptitiously all data contrary to the investigator's hypotheses in a box for burial.

❤ Clinical trial: malpractice suit.

❤ Data cleaning: eliminating dirty data that will make scatter plots scatter and p-values nonsignificant.

❤ F-distribution—the proportion of students flunking Intro to Stats.

❤ Histograms: plots that cause sneezes and other allergic reactions in researchers.

❤ Logistical regression: a way of figuring out the logistics of getting your study accepted into JAMA.

❤ Nonlinear regression: what happens to the behavior of an investigator in the midst of preparing a grant submission.

❤ P-value: results of urinalysis.

❤ Survival analysis—strategizing how to get the most money from the funding agency so that your research center doesn't fold.

❤ Zzzz-distribution—the proportion of students staying awake in Intro to Stats.

❤ Principal proponent's analysis—figuring out what the principal investigator for the study wants to find. Alternatively, figuring out what the main supporter of the grant on the funding agency's review committee wants to hear.

*Meredith G. Warshaw, Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC), spent 10 years as a biostatistician doing psychiatry

Today's Thought

A medium, so called because it is neither rare nor well done—Ernie Kovacs

A committee is a group that keeps minutes and loses hours—Milton Berle

Thin people are beautiful but fat people are adorable—Jackie Gleason

From the Desk of the Editorial Working Committee

REGIONAL ACTIVITY

Taiwan

By C. Andy Tsao

Reaching Out: Trends, Organizations and Information Sharing

As in other part of the globe, the profession of statistics in Taiwan is in the process of redefining itself in the past few years. Some application domains are emerging astoundingly, for example, bioinformatics, data mining and biopharmaceutical industries. Their fast development often presents challenges and opportunity for statisticians. New organizations are established to serve these demands.

Center of Drug Evaluation (CDE), Department of Health Established in 1998, CDE plays a pivotal role in upgrading the efficiency and quality of the drug evaluation process and providing proactive support for Biotechnology and Pharmaceutical Industries in Taiwan.
URL:
http://www.cde.org.tw/english/english.htm

Protech Pharmaservices Corporation Founded in 1997, PPC is now one of the most established integrated CRO companies in the Asia-Pacific area. URL: http://www.ppccro.com/

Chunghwa Data Mining Society (CDMS)
URL: http://cdms.stat.fju.edu.tw/

Journal of Data Science (JDS)
Do you think that statistics might well be renamed as "data science" and good applications and good problems should be of focus rather than just "good math"? If you think so, you are not alone. Here is a new journal dedicates to data science.URL:http://mpd.pagras.net/~mtchao/JDataScience/JDS-0.html

Hong Kong

By Hailiang Yang

Here I report some of the activities of 2002 from the Hong Kong statistical community. I apologize for any missing information.

International Conference on Applied Statistics, Actuarial Science and Financial Mathematics: The University of Hong Kong and The Hong Kong Polytechnic University are jointly organizing an International Conference on Applied Statistics, Actuarial Science and Financial Mathematics. This conference is to be held at the University of Hong Kong (December 17, 2002) and the Hong Kong Polytechnic University (December 18-19, 2002).

The chairmen of the organizing committee are Dr. K.W. Ng and Professor K.L. Teo and the chairmen of the scientific committee are Professors Elias Shiu and Howell Tong. Many leading experts and distinguished speakers will give invited talks, among whom are Hans Gerber, Marc Goovaerts, Tze Leung Lai, and Harry Panjer. http://web.hku.hk/~icaaf/

Workshop on Probability with Applications to Finance and Insurance: This workshop is to be hold at the University of Hong Kong from July 15-17, 2002. The members of organizing committee are: Inchi Hu, Bing-Yi Jing, Tze Leung Lai, Qi-Man Shao, Hailiang Yang, and Siu Pang Yung. More than 30 experts in both theoretical and applied probability are invited to given a talk. The workshop is initiated by Professor Tze-Leung Lai. Prof. Lai will visit the University of Hong Kong as C.V. Starr Professor from June to July 2002. http://www.hku.hk/math/

WELCOME NEW MEMBERS

We would like to welcome new members who joined between January and June 2002.

Garish Aras	Chris Assaid	George Avirappattu	Warren Bao
Airong Cai	William Brady	Chen Chen	Jingru Chen
Aili Cheng	Danny S. Chiang	Darstein Christelle	Teng-Chiao Chu
Jin Ding	Andrea Dynder	Tara Erb	Vladislan Fishman
Tracy Gmoser	Shu-Pang Huang	Yangxin Huang	Mohammad Huque
Manzoor Hussain	Xinwei Damal Jia	John G. Jiang	Hann-Chang Jou
Yong S. Paul Kim	James Lee	Dong Li	Haihong Li
Jennifer Li	Zhiyuan Liang	Chengan Liu	Jason Liao
Yuming Liao	Genzhou Lin	Xianqun Luan	Bret Musser
Rathoug Paul	Barry Rosen	Jiahe Qian	Amy Qin
Lei Shen	Fan Shi	Synthia O. Siu	Xiaowu Sun
Yuhwen Soo	K. Linda Tang	Chi-Hse Teng	Lan-Feng Tsai
David A. Van Dyk	Joel Waksman	Hansheng Wang	Lixia Wang
Wenjin Wang	Guodong Wu	Jianrong Wu	Zhihua Xiang
Yang Xie	Jin Xu	Paul Zhang	Zuoshun Zhang
Lue Ping Zhao	Huaqing Zhao	Jun Zhao	Bei Zhou
Honglin Zhou	Wenjiong Zhou		

MEMBERS' ACTIVITIES

News from ICSA Members

Dr. Robert T. O'Neill, Director of the Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, is the recipient of the 2002 Marvin Zelen Leadership Award in Statistical Science. This annual award, supported by colleagues, friends and family, was established to honor Dr. Marvin Zelen's (The Department of Biostatistics at the Harvard School of Public Health) long and distinguished career as a statistician and his major role in shaping the field of biostatistics. The award recognizes an individual in government, industry, or academia, who by virtue of his/her outstanding leadership, has greatly impacted the theory and practice of statistical science.

Professor Kung-Yee Liang, Department of Biostatistics, Johns Hopkins University, was elected as an Acadamic Member for the Academia Sinica, Taiwan on July 4th, 2002. One of Dr. Liang's major research contributions to the statistical and biomedical community is his work, co-authored with Professor Zeger, on Generalized Estimation Equations (GEE), an innovative tool for analyzing longitudinal and other types of correlated data.

Professor Ruey Tsay, Graduate School of Business, University of Chicago, was elected to as an Acadamic Member for the Academia Sinica, Taiwan on July 04, 2002. Dr. Tsay has made many important contributions in time series analysis, especially in the area of financial econometrics.

International Chinese Statistical Association
Profit & Loss
January through June 2002

Ordinary Income/Expense	
Income	
Advertisement	200.00
Contributions Income	
Unrestricted	100.00
Total Contributions Income	100.00
Membership Dues	5,925.00
Total Income	6,225.00
Expense	
Casual Labor	46.50
Internet Registration	35.00
Licenses and Permits	20.00
Membership due refund	400.00
Postage and Delivery	
Bulletin	2,518.96
Other	392.67
Total Postage and Delivery	2,911.63
Printing and Reproduction	
Jan. Bulletin	4,602.50
Total Printing and Reproduction	4,602.50
Professional Fees	
Tax filing	431.80
Total Professional Fees	431.80
Supplies	
Other	144.14
Total Supplies	144.14
Web Page Hosting	1,200.00
Total Expense	9,791.57
Net Ordinary Income	-3,566.57
Other Income/Expense	
Other Income	
Interest Income	644.57
Total Other Income	644.57
Net Other Income	644.57
Net Income	**-2,922.00**

International Chinese Statistical Association

Balance Sheet

As of June 30, 2002

International Chinese Statistical Association

Balance Sheet

As of June 30, 2002

ASSETS	
Current Assets	
Checking/Savings	
checking	4,014.45
Savings-CD	31,164.84
Savings-Money Market	35,653.42
Total Checking/Savings	70,832.71
Total Current Assets	70,832.71
TOTAL ASSETS	**70,832.71**
LIABILITIES & EQUITY	
Equity	
Opening Bal Equity	81,934.16
Retained Earnings	-8,179.45
Net Income	-2,922.00
Total Equity	70,832.71
TOTAL LIABILITIES & EQUITY	**70,832.71**

INTERNATIONAL CHINESE STATISTICAL ASSOCIATION

Membership Application / Renewal Form (2002)

Date _____

NAME (Last) (First)

English:

Chinese:

ADDRESS

Office:	Home:
City: State:	City: State:
Zip:	Zip:
Country:	Country:
Tel (O):	Tel (H):
Fax (O):	Fax (H):

E-Mail Address:

Highest Degree: Year Graduated:

University: Occupation/Title:

MEMBERSHIP FEES

Regular US$40	_____
Student US$20	_____
Permanent US$400	_____
Spouse (50%)	_____ (Spouse Name _____)
Biometrics (Free)	_____
Donations	_____
Total Amount	_____

STATISTICAL AREA OF INTEREST (circle as many as you like):

A. Agriculture	F. Health Sciences
B. Business/Econometrics	G. Probability
C. Computing/Graphics	H. Social Sciences
D. Education	I. Theory And Methods
E. Engineering	N. Biostatistics

Please make checks payable to I.C.S.A.

Mail this form and a check to: **ICSA c/o Yi Tsong, Ph.D.**
13215 Lazy Glen Lane
Herndon, VA 22071
U.S.A.
(tsong@cder.fda.gov)

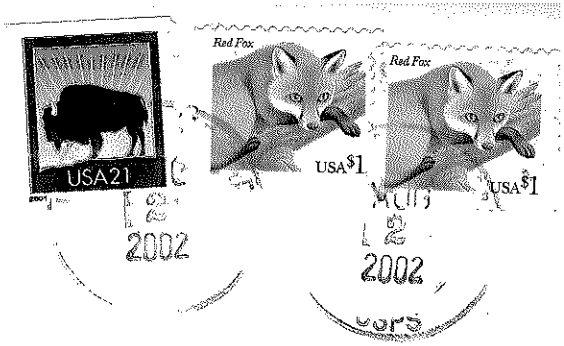
INTERNATIONAL CHINESE STATISTICAL ASSOCIATION

Information Sheet (2002)
Date _____

RECENT NEWS: (publications, research or teaching activities, job transfer, awards or honors received, etc.)

SUGGESTIONS :

I. C. S. A.
13215 Lazy Glen Lane
Herndon, VA 22071
U.S.A.



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