International Chinese Statistical Association

http://www.icsa.org

泛華統計協會

Features:

- Interview with a Distinguished Statistician
- Clinical Trial for Drug Development
- Contemporary Statistical Issues
- Meeting Announcements
- Career Opportunities

Bulletin January 2005

Chinese Chess

Chess is one of the four arts in ancient China to symbolize the classic scholarship. The history of Chinese chess game can be dated back to about 4000 years ago. The chess game was evolved from the strategies of ancient warfares in Chinese history. Today, it still remains as one of the most popular intellectual competitions.

From the Editor

Kao-Tai Tsai, Ph.D.

When I first saw these words in Taiwan about 20 years ago, it did not quite strike me. However, it is a very different feeling today. It is very unfortunate that, in two consecutive issues of the ICSA Bulletin, I have to report to you that ICSA lost two great friends and strong supports. Professor C.Z. Wei, a great researcher in many areas of statistics, passed away in a young age after years of courageous fight against cancer. As sad as it is, however, it is inevitable to have these kind of events happening upon us. The more important aspect for the ICSA is to pass the torch to the next generation to make this organization even stronger and more prosperous.

In this issue, we present an interview with Professor Xiru Chen in China. It is important for us to provide the members the opportunities to listen to the experience of great statisticians from different parts of the world about their research and how statistics had been applied in their parts of the world. We will try to continue this effort in the next issue. We are also very fortunate to have Professor Lai shared with us his recent research in clinical trials for drug development. It is both interesting and beneficial to know the insights of these wonderfully accomplished friends.

The ICSA 2005 Applied Statistics Symposium is under preparation by our members in the Washington D.C. area. The preliminary program is inside this issue, and the more up-to-date information can be found in the ICSA website (http://www.icsa.org). We also post a couple of career opportunities in Taiwan inside this issue as part of our service to the members. We are extremely grateful for their support and would like to encourage other members to follow their examples.

We hope you enjoy the fruit of our labor in this issue. And, as usual, your help and contribution in any ways will be greatly appreciated.

Finally, on behalf of the editorial team, I would like to sincerely wish you a very healthy and prosperous new year ahead.

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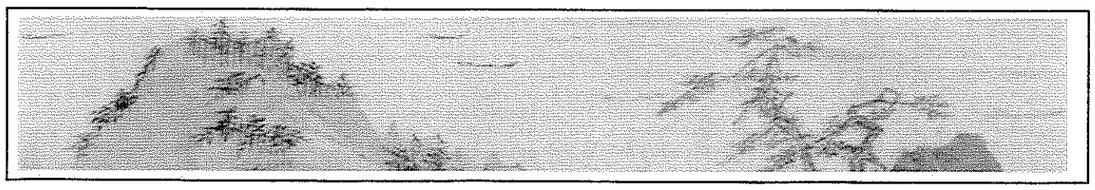

Committee Chairs
ICSA, 2005

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Submission Guidelines
ICSA Bulletin

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

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

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

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

Questions
Please submit your questions to the Editor by email at tsai0123@yahoo.com.

For the complete list of Committee Members and terms, please go to the ICSA website: www.icsa.org.

From the President

Jiahua Chen, Ph.D.

There have been only a few unexpected outcomes that have occurred in my life. One of them was being elected as the President of the International Chinese Statistical Association for the year of 2005. It is indeed a great honor to be elected as the President. I highly appreciate our ICSA members for their trust and confidence in me.

During the entire past year, I have been the president-in-training, warming myself up and setting myself in the right mindset for this important position. Time goes by so fast and all of a sudden, my term is about to start. It is an overwhelming challenge for me to be the President of the ICSA. In fact, I was not so sure that I would have the courage to take the challenge and the ability to turn the challenge into opportunity until I secured the previous president Dr. Frank Shen's promise to be on call during my term. In addition, our past-past president, Dr. Zhiliang Ying has been very generous to me with his advice in a number of issues during the past year. I am also very delighted that Dr. Ivan Chan has agreed to continue to serve as our executive director. Last but not the least, my courage and confidence is reassured by the pool of a large group of enthusiastic members who have served the ICSA in the past in various capacities, and would surely continue to do so in the future.

Although the ICSA is still young in its age, its influence has been felt and noticed worldwide. The ICSA has established a pivotal position internationally in the statistical society and made significant contributions to the field of statistics and probability accordingly. The ICSA's official journal, *Statistica Sinica* has risen rapidly to an enviable level in term of its impact to the academic community, according to the report of ISI Journal Citation. All these successes are due to the strong leadership of the Presidents in the past, to the thousands of productive members whose research has always been cutting edge, to the innumerable dedicated members who play crucial roles in the statistical education and applications, and to our founding members whose vision has led the ICSA to its robust growth since its birth and suitably outlined the ICSA's scope for future.

So now what? It is certainly not the time for wine or fireworks and we all need to continue working hard to consolidate our success and explore new revenues to improve the popularity of ICSA. Here are some concrete things in my mind.

First of all, I wholeheartedly agree with the previous president, Dr. Frank Shen that the most vital issue to any organization is its membership. Without energetic members, no organization can maintain its survival. A large number of new members are recruited each year during the ICSA's applied statistical symposium and the joint statistical meetings. The membership committee has been very active in encouraging their colleagues, collaborators and academic friends to join the ICSA. We owe to these activities and efforts to reach the current membership scale of the ICSA. On the other hand, we all notice that our membership is geographically biased and the membership rates in some regions including the North America, our most important power basis, still have substantial room to improve. I would like to invite everyone to contribute their ideas and suggestions on the membership improvement to our membership committee chair, Dr. Jun Zhao (J.Zhao@organonusa.com).

In the past year, under the leadership of Dr. Frank Shen, a task force was formed to re-invent the ICSA's web site. We can then add some important features to the web site such as on-line membership application, automatic membership renewal and on-line charge for membership dues. I believe that these features are helpful for membership retention and new membership recruitment, and provide great convenience to

our members, particularly to those living outside the North America.

During my visit to some universities in mainland China this year, I was often told that one obstacle for mainlanders to join the ICSA is the currency inconvenience for membership dues due to the control of hard currency. (Incidentally, I also heard the similar concerns from some members in other regions). According to the recent news, it seems that the green buck is losing its shine to other currencies. I hope that the currency problem will soon no longer be an obstacle. Yet reformation leading to convenience of membership dues will undoubtedly help membership growth of the ICSA. If you have any ideas or suggestions in this respect, please do not hesitate to let me know.

I have nearly completed the committee appointment task. About 50 members have cheerfully agreed to serve on the ICSA committees. I am very much grateful to them. Due to my limited range of contact, however, there must be many capable members who are willing to serve, but I failed to enlist. I cordially invite and welcome you to contact me if you would like to engage in the committee work. I will be more than happy to get everyone involved. The members from under-represented groups and regions are particularly encouraged.

The board of directors is the virtual governing body of the ICSA. One third of the directors are to be replaced each year by newly elected members. If you would like to engage in management and practice your vision toward the development of the ICSA, to serve in the board of directors may be the best avenue. Please contact the nomination committee chaired by Dr. Xuming He (x-he@uiuc.edu) for nomination and election matters.

The applied statistical symposium will be held in Washington D.C. June 19-22, 2005. Drs. Yi Tsong (TSONG@cder.fda.gov) and James Huang are in charge of the symposium program. The next ICSA symposium will be held in Taipei in 2007. We are grateful to Professor C.S. Cheng for being willing to be in charge of the 2007 symposium.

Finally, thank all of you again for placing trust on me unconditionally. I count on the support from each and every one of you and look forward to serving for, working with, and hearing from you.

Jiahua Chen, President, ICSA

Jiahua Chen, Ph.D. is a Professor of Statistics at the University of Waterloo, Ontario, Canada. Email: jhchen@uwaterloo.ca

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From the Executive Director

Ivan S.F. Chan, Ph.D.

ICSA had a successful year in 2004. We held two well-attended statistical meetings: Applied Ssymposium in San Diego and the International Conference in Singapore. These activies provided tremendous opportunities for scientifc exchanges among statisticians working in academia, government, and industry. We sincerely thank the organizing committees for their dedicated efforts. We also held two very productive board meetings dicussing many important issues concerning the operation and future development of ICSA. We thank Frank Shen (ICSA President, 2004) for his leadership, and we also thank the board members for their generous support.

This year we started to implement electronic voting for ICSA officers: 2005 President-elect, 2005 Biometrics Section Chair, and 6 members of the Board of Directors for 2005-2007. Election ballots were sent to all members via email (or mail if no valid email address is available). Members were encouraged to return their votes by email. Votes were counted by computer programs that were developed and validated by an independent team of 3 volunteers: Drs. Jacksen Lou, Joshua Chen, and Bill Wang. As part of the vote count, a statistical sampling-based QC check was performed to ensure the accuracy of the vote count. The results (see Table 1 below) have been announced at the Members Meeting at the JSM in Toronto and on the ICSA web. I would like to express my sincere thanks to all of the candidates for their enthusiasm and support of ICSA, to the nomination committee for their great coordination, and to the volunteer team for helping with the electronic vote count. I would also like to congratulate and welcome the newly elected officers. As a separate note, there are 5 board members whose term ended in 2004 (Zhiliang Ying, Sue-Jane Wang, Zhaohai Li, Heping Zhang, Rong Chen). We thank them for their tireless efforts and generous support over the past 3 year, serving on the ICSA board.

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

Best wishes to all of you in 2005.

Ivan S. F. Chan, Executive Director, ICSA

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Reports From Committee Chairs

Program Committee

By: Naitee Ting, Ph.D.

We had a very successful 2004! The June Applied Statistics Symposium in San Diego was well attended, with a 4-day program, attracted close to 270 participants including long-term members, new members, and non-members. Please refer to the July 2004 Bulletin for additional details. The efforts from the symposium committee (co-chaired by Nancy Lo and Gang Li) and the outcomes of the 2004 symposium were exceptional! In July, the sixth ICSA International Conference took place in Singapore. With the great effort from the Conference Committee (co-chaired by Zhiliang Ying and Louis Chen), the 2004 conference was also a big success. Please refer to the article in this issue of Bulletin from Dr. Yiu-Man Chan for details. During the August JSM at Toronto, Jiahua Chen led a local committee to help set an ICSA booth, and organize the membership meeting as well as the ICSA annual banquet. The ICSA booth attracted many many visits from interested Chinese and other statisticians. In fact, a large number of them joined the ICSA during the period. There were over 100 people went to the banquet. Dr. Fritz Scheuren, the ASA President-Elect, also joined the banquet to show his support of ICSA activities. On behalf of ICSA Program Committee, I would like to express our sincere appreciation to the committee chairs/co-chairs (Nancy, Gang, Zhiliang, Louis, and Jiahua) as well as committee members who worked so hard to make all these events successful.

Looking ahead in the coming years, ICSA plans the following programs for our members:
(1) The 2005 Applied Statistics Symposium will take place in Washington, D.C. The 2005 symposium committee is organized by Yi Tsong. Details regarding this symposium will be announced in the near future. Please visit the ICSA web www.icsa.org to look for update information.
(2) ICSA and The International Conference on Multiple Comparisons (MCP) co-sponsor the 2005 meeting at Shanghai, China. The committee is co-chaired by Jason Hsu and Ajit Tamhane. The MCP 2005 web is www.stat.ohio-state.edu/~mcp2005/, please go to the web for more information. We encourage all ICSA members to support MCP 2005.
(3) The program committee proposes to hold the 2006 Applied Statistics Symposium at Connecticut. Details will be worked out in the near future. This symposium will be co-organized by Greg Wei and Ming-Hui Chen.
(4) The program committee proposes to hold the seventh ICSA International Conference at Taiwan in 2007. This conference will be coordinated by Ching-Shui Cheng.
(5) The program committee proposes to hold the 2007 Applied Statistics Symposium at North Carolina, to be co-organized by Shu-Yen Ho and Danyu Lin.

Naitee Ting, Ph.D. is an Associate Director in Biostatistics, Pfizer Global Research & Development, New London, CT 06320, USA
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Book & Journal Donation Service *By: T. Timothy Chen, Ph.D.*

Since 2000, Dr. Chen has served as the chairperson of ICSA Book and Journal Donation Committee, which facilitates the shipment of books and journals to the university libraries in the developing countries, including China, Nigeria, Kenya, India, and Pakistan. Over the years, ICSA has paid the mailing cost of $3469.38 to send out more than 3500 pounds of books and journals. He wants to encourage ICSA members to continue donating their books and journals. Interested members should write to him at tar_timothy_chen@yahoo.com.

Tar Timothy Chen, Ph.D., former president of ICSA (1999), is the Chinese pastor of Saint Louis Chinese Gospel Church at 515 Meramec Station Road, Manchester, Missouri 63021. Church phone number is 636-391-2112 and webpage is http://www.stlcgc.org.

In Memory of Professor Ching-Zong Wei

By: Institute of Statistical Science, Academia Sinica

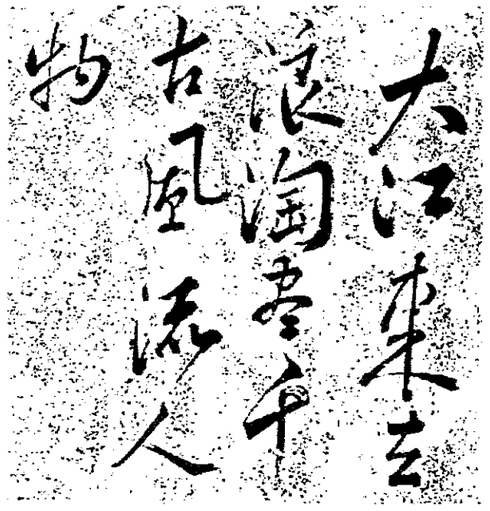
Professor Ching-Zong Wei (1949-2004), Research Fellow of the Institute of Statistical Science at Academia Sinica, Taiwan, passed away on November 18, 2004 after a six-year courageous fight with brain tumors (including three major surgeries). He is survived by his wife of close to 30 years, Mei, and a daughter.

Ching-Zong was born in 1949 in south Taiwan. He studied mathematics at National Tsing-Hua University, Taiwan, where he earned a B.S. degree in 1971 and an M.S. degree in 1973. Professor Y.S. Chow successfully persuaded him to pursue advanced studies at Columbia University where he earned a Ph.D. degree in statistics in 1980, under the guidance of Professor T.L. Lai.

Ching-Zong joined the Department of Mathematics at University of Maryland, College Park, as an Assistant Professor in 1980, and was promoted to the rank of Associate Professor and Full Professor in 1984 and 1988. In 1990 when he returned to Taiwan, his beloved homeland, he joined the Institute of Statistical Science at Academia Sinica where he stayed for the rest of his life, including the period of 1993-1999 as Director of the Institute. His leadership and vision greatly helped the Institute grow, expand and diversify. He also held a joint appointment with the Department of Mathematics at National Taiwan University.

Ching-Zong made fundamental contributions in the areas of stochastic regression, adaptive control, nonstationary time series, model selection and sequential design. In particular, his pioneering works on (i) strong consistency of least squares estimates in stochastic regression models (with T.L. Lai), (ii) asymptotic behavior of least squares estimates in unstable autoregressive models (with N.H. Chan), and (iii) predictive least squares principles in model selection, have been influential in the control engineering, econometrics and time series literature. Ching-Zong was elected a Fellow of the Institute of Mathematical Statistics in 1989, and served as an Associate Editor of the Annals of Statistics (1987-1993) and Statistica Sinica (1991-1999). He was on the list of highly cited researchers identified by the web site ISIHighlyCited.com.

In addition to theoretical research work, Ching-Zong was deeply concerned about statistical education. To promote statistical thinking among the general public, he published in local newspapers and magazines articles on various topics of general interest such as lottery games and the Bible code. These articles, written in Chinese, introduced basic statistical and probabilistic concepts in a heuristic and reader-friendly manner via entertaining stories without formal statistical jargon. His impact on statistical education in Taiwan will be felt for years to come. We will miss him dearly.



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STATISTICA SINICA

Volume 14 Number 4 October 2004

Interview with a Distinguished Statistician

A Conversation with Professor Xiru Chen (陈希孺院士)

By: Professor Y.G. Zhang

我代表编辑部来对您做一个人物专访，想请您谈一下您研究统计学的经历和贡献及对统计学的一些看法。请您随便来谈。

Q1：中国统计学研究开始的时间比西方晚，在您上大学时国内还没有统计专业，更谈不上有研究工作，想请您谈一下是怎样开始了统计学研究的。

A：其实我开始搞统计，纯粹是组织的分配。我在大学时没有学过概率与统计课程，我就读的武汉大学当时没有人搞这个。大三暑假在家读了格涅坚科的“概率论教程”，那时并不是想今后就要搞这个，只是因为假期中不能什么都不干。看了这本书后兴趣很大，可以说，我对概率统计的入门是从这本书开始的。毕业后分配到中科院数学所工作，所领导把这一年来所的毕业生大都分配到概率统计组里，这是因为此方向是当时十二年科学规划中数学三个重点方向之一（另外两个是微分方程与计算数学）。我们是从零开始。当时王寿仁先生指定我们读两本书，一是费勒（Feller）的概率论及其应用，另一本是哈尔莫斯（Halmos）的测度论，同时，张里千先生在北大开了一门初等数理统计的课，我们也去听。到57年我读了克拉梅尔（Cramer）的《统计与数学方法》，这可说是我系统学习数理统计理论的开始。

1956年是以著名的“双百方针”为标志的、政治上比较宽松的一个时期，我因这个机缘，得入选于1957年10月去波兰留学一年，

师从M.Fisz教授，至58年10月回国，历时一年，在这一年中，除去学习波兰语的几个月外，其余时间，大多花在其它活动上。如参加修建新大使馆的劳动和搞政治运动等，业务上收获不大。回国后，数学所的概率统计组已扩充为一个研究室，内分概率、统计两个组。前者当时被认为是从事一些“尖端”性质的研究，我被分配到了统计组。可以说，我以统计学为业，是从这时开始。

我搞统计学起步晚，起点也低，还有一个重要的缺陷，即由于历史与现实的原因，统计学当时在中国是纯粹作为数学的一个分支来看待的，对其应用上的多样性，了无所知。58年“拔白旗”，强调联系实际。以任务带学科等，蔚然形成运动，对这一段的做法，后来颇多诟病，但个人认为，它不无正面意义，主要是使我们搞统计的人初步树立了“统计学贵在解决实际问题”的思想，当时，国内应用统计方面的读物很少，记得当时室里从外面弄来一些农医科的统计课教材。我的“应用统计启蒙”，就是从学习这些教材开始。

我回国近半年后，于59年3月，与所里十余位研究人员一起，被下放到革命圣地延安南边百余公里，陕北高原上某村庄。作为“改造世界观”的一种形式，为时10个月，60年1月回所后到当年夏天，国内又处在一个新的“大跃进”时期，就我个人而言，这半年在业务上可以用“无所事事”4个字来形容。

1960年8月我被调到2年前建立的中国科技大学数学系任教，这对我来说是一个转机，。虽然当时因三年困难而导致的物质生活甚为困苦，但由于学校的具体环境其它干扰较少，还可以安心工作，我在那时起到66年文革前，除了繁重的教学工作外，还读了几本概率

统计方面的重要著作，包括 Loeve，Doob，C.R.Rao 和 Lehmann 等的著作，打下了一个比较过得去的基础，另外，从 62 年下半年起，参加了成平先生在数学所主持的一个研究参数估计的讨论班，我在其中学到不少东西，包括怎样找研究题目和如何从事研究等，从这一点说，成平先生可以说是我进入研究工作的领路人，自那时起我先后发表了十多篇论文，内容涉及参数估计、区间估计、统计判决与非参数统计等方面，这一良好的发展势头，随着 66 年文革风暴席卷中国大地而戛然中止。

我重新恢复教学和研究工作，是在 70 年代后期，文革这 10 年白白浪费了。学问如逆水行舟，不进则退。说句公平话，也不能全怪文革。回想起来，文革 10 年中可以利用搞业务的时间还是有的，只是当时自己受到“读书无用论”的影响，看不到前途，鼓不起劲。十年一觉醒来，发现形势已经大变，统计学理论往深、广的方向发展，新分支，新领域层出不穷。而为进入研究工作，门槛也大为提高，我经过努力，也取得了一些局部的成绩，但总体上看不能令人满意，多年的耽误造成学术根基上的缺陷，从事研究工作最佳年龄段的虚度，终究是一个难于弥补的遗憾。

QII 您从事统计研究已经几十年了，您能否对中国近二、三十年来统计的发展作一回顾和评价？

A：我也曾考虑过这个问题。总的说，我认为这还是进展比较大的时期，尤其是与文革以前中国数理统计很薄弱这个情况比较，更是如此。这从一个事实可以看出来，在 79-83 年这 5 年，我们每年都举办一个暑假讲习班，讲一些基本的东西，来的人很多，其中不少现已成为统

计界的元老和骨干，当时就连他们也还只是处于一个重新起步的阶段，可见当时的整个水平了。当时能写出比较好的数理统计论文并能在重要杂志上发表的，屈指可数，在年青人更是稀少。这因为在文革前，大学数学系，除了少数几个以外，都没有数理统计这门课。当时也没有正规的研究生制度。另外，在文革前，中国处在闭关锁国时代，人们对国际上的动向知道得很少，这种状况直到 1980 年代才有了较大的改变。

所以，当文革结束时，中国的数理统计学队伍小而弱，实在是其来有自。以此作为对比，这 20 余年的进步，算得上很显着。例如，现在有了专业的统计学会和统计专业刊物，在若干大学中开办了有关的系，具有一定数量和质量的教学和研究队伍。在人才培养方面，建立了正规的学位制度，有不少青年人脱颖而出，有的已成长为国际知名的统计学家。从理论研究成果看，国内学者中发表过有较高质量的论文的人数，有了显着的增加。不少论文发表在国际排名前列的几种刊物上，所研究的问题也多能与当前的国际前沿接轨，不足之处是跟踪性质的研究多，具有独创性以至能影响学科发展方向的工作还绝无仅有。在应用方面，初期大多集中在工业统计，包括试验设计，产品检验，可靠性，质量控制与统计优化等方面，取得了不少富有经济或社会意义的成果。近年来关注生物统计和金融、保险方面的逐渐增多。

在看到这些成绩同时，我个人觉得，与国际先进水平比，中国的统计学不论从理论或应用方面看，都还有不小的差距。关于中国近代科学落后的原因，论者很多，远的从中国文化的特点上立论，谈近一些，我认为像统计这样一门应用性很强的学科，其发展不能脱离外部

环境的制约。中国目前的社会和经济状况还不足以使人们对统计学的重要性有充分认识，社会对统计方法还没有足够的需求。在统计发达的国家，对这门学科的应用价值已经得到广泛的承认，这给学科提供了发展的基础。但在中国，由于这一点的缺失，学科发展缺乏一个充分的外部支持。例如不论是在工业企业或实用研究单位，认为需要聘用统计人才的还很少，所以搞统计的人就业面还比较窄。只有当社会上充分意识到统计方法的重要性时，这门学科在中国才能有比较大的发展。缺乏外部支持导致统计研究经费的拮据，研究生大多只能从自然科学基金取得一些经费，来自工业企业和其它应用部门的还很少。当然，问题是两面的，统计学家不能一味抱怨外部支持不够，不能坐等外部环境的改善，也应看到，由于我们统计学家未能提供质高量大的应用成果，也就难于争取到社会的支持，这正是我们应当努力的地方。

在我国，由于历史和现实的原因，对统计学工作的评价基本上仍以其数学水平为标准，这使应用统计的工作难于得到应有的鼓励和重视。在中国统计学界内部，颇有一些人认为这是妨碍统计学发展的一个原因，并主张对统计工作采用符合本学科特点的评价标准，我个人认为这种意见的合理性不容置疑。但仍认为，问题的根子不在此，而在于我上面提到的，更深层的原因还是因为统计应用没有真正发展起来，没有得到社会和市场的认可，因此就缺乏足够的基础去树立一个按本学科特点而设计的评价标准，只好仍委之于数学。要改变这种情况，还须从根本处着手，人为地改变一下评价标准不一定能妥善解决这个问题。当然，一定的匡正措施是可以而且应该考虑的。

QIII：去年您刚刚过了七十华诞，中国科技大学您的学生们还把您的论文编辑出版了，请您概括介绍一下您的主要成果。

A：前面我已讲过，自己起步比较晚，加上长期荒废，作出的成果有限，文革前作的一点工作已如前述，七十年代后期以来，比较系统研究了线性回归的大样本理论，由于模型简单，许多问题可以作得比较深入，有的可得出充要条件，我在这方面做的工作包括 Gauss-Markov 条件下以及只假定误差 r 阶矩（$1\leqslant r<2$）存在时，最小二乘估计强弱相合性的条件问题，后者在一定意义下得出了充要条件，对线性回归误差方差估计的分布收敛于正态的问题，在最优的矩条件下，得出了理想的速度 O（$1/\sqrt{n}$），往后研究过回归参数的最小一乘法和 M 估计的相合性和渐近正态性，这些问题一直搞到 90 年代后期。这 20 年间在这个领域花了比较大的精力，所获成果曾在 C.R.Rao 1995 年出版的一本专着中列为一些定理，在 2002 年北美统计学会选我为 Fellow 时提及了这一个方面。另外一个方面是在非参数统计方面的工作，其中包括 U 统计量的渐近性质。1978 年解决了 U 统计量分布的一致性收敛速度为 O（$1/\sqrt{n}$）。我与赵林城合作，在 1982 年得出了最优的非一致速度 O（$n^{-1/2}\left(1+|x|^3\right)^{-1}$）。一位苏联学者的专著导言中提到了这个工作。关于非参数回归我还做过一些关于密度估计、非参数回归估计和判别问题，有的得出了最优的收敛速度。其它关于秩序统计量，经验 Bayes 和判决函数，广义线性回归，EV 回归等方面的研究都有所涉及。我的工作基本上属于纯数学的性质，这多少反映了我这一辈中国统计学者中许多人所共有的局限性，以及中国统计学在那一阶段发展的一个特点。

QIV　您个人除去对统计方面有很深的造诣外，在文学历史政治等方面都有广博的知识，这些和您搞统计研究有关系吗？还是纯粹的个人兴趣？

A：可以肯定说这与我搞统计这个专业无关，而是出于家庭及社会的影响，我从小长在农村，比较落后闭塞，琴棋书画等都不会，只剩下读书。我父亲早年就读于长沙一个工业学校，他属于“五四”后的“激进青年”那一类的人，喜读书，发议论和谈国事，家里订有报纸杂志，各种新旧书籍也不少。我从小就读了一些，这对我日后的思想和性格的形成不无影响。我生下来不久即逢八年抗战与三年内战局势一直动荡不安，也促使人去关心和思考一些问题。

我读书多，但属于“泛读”的性质，无所专长，一部分是业余消闲性质，一部分也是为了认识世界。例如，中国和世界何以演变成现在这个样子，未来的发展趋势如何？这有其以往的轨迹可寻，这就要求了解历史。98 年是戊戌政变一百周年，围绕这个题目发表的论著很多。我明白，这都是着眼于当前中国改革与转型的现实，所谓“一切历史都是当代史”，在此得到了印证。除历史著作外，我喜读的一类书是纪实性作品，即在西方归“non-fiction”的那一类，例如丘吉尔的多卷本《大战回忆录》，我都细读过，可惜这样的好书不多。纪实作品帮助我较深度地了解中国及世界的现实，以弥补报刊杂志上浅层次报导的不足，问题是这类作品中所引资料的准确性，往往颇有问题。传记类作品我看得也不少，我印象是，这类著作，愈远离当前，质量愈高，因为中国有“为尊者讳，为亲者讳，为贤者讳”的传统。文学、哲学、作品，中国的读得较多一些，西方哲学，尤其是德国古典哲学，

思辨性太强，非我理解所能及。

我相信“开卷有益”的说法，我几十年来在历次政治运动中倍受冲击，都能以平和的心态对待，这与我从广泛的阅读中所获得的教益与启示不无关系。另外，多阅读也有助于提高文字表述能力，当前在理科学生中，不少人在这方面的表现不尽人意。

QV：下边请您读一下人才培养问题，我们老一辈出了不少人才，可是我们这一辈出的人才不太多，您是否可以分析一下原因呢？今后我们如何才能改善这个局面呢？

A：我有些看法与其它人可能有些差异。如我在前面曾提及的，外部环境是一个制约因素。恩格斯曾经说过，社会上的需要比办一百所大学更能促进科学的发展。当前统计人才出得不多，一个重要原因是没有足够的社会需求，我们当前处在一个转型的时期，有很多更大的问题需要解决，不少企业为这些问题所困扰，无暇顾及像统计方法应用这类技术性的问题。科研部门的经费也比较紧。统计学在某种意义上说是软科学，它不像技术是可以应用马上就见效，它往往需要与其它“硬学科”配合后应用到某种问题上，才能起作用。统计方法的这个特点使统计学家不易参入到较大型的项目中去。统计学当然不能算是软科学，但它起作用的方式是相近的，可以说，因此其社会需求的建立就比一些能发挥“立竿见影”效果的技术性科学更难。而当社会需求达不到时，要学科有大发展是不可能的。拿美国的情况说，在 1930 年代美国的统计学还不算发达，直到二战后由于实用需要，而美国的社会机制又能使这种需要很快引导到人才上的需求，统计学和统计教育才很快发展起来。中国目前还达不到这个状态，而只从学科

内部去考虑学科发展及人才培养，不能根本解决问题，我的意思并非是要坐着等到时机到来，而是要促进大环境的到来，要促进统计在应用上有更多的表现。至于在统计教学上，我觉得目前国内还基本上是延续以数学为中心那套方式，有的把纯数学的份量减轻一点，但如何结合统计学自身的特点去设计课程和培养方式，似乎还没有探索到一套成熟的经验。因此弄得不好可能产生这样的后果，统计系学生在数学和统计理论上学得少了，但在应用统计的学习上也没有本质的加强。这样一来哪一方面都不占优势。目前国内统计系偏重金融保险等专业方向的很多，但我觉得这方面也要有慎重的考虑。例如这方面的人才需求有多大？我们的教学力量、教学内容能否跟上等？在这方面思路应再宽一点。另一方面，考核过于量化且频繁，不利于安心坐下来深入搞研究，这对年青人的压力就更大了。对年青人简直是一个饭碗能不能保的问题。在中国当前的现实，这个问题很令人困惑，不管哪种办法都存在问题。考核太多会产生短期行为。但如放松考核，结果他连经常本职的工作都没做好，而把主要时间和精力放到外边兼职挣钱去了，这也岂不更乱了？这问题人们议论很多，也没有产生出一个有可行性的好办法。关于对人的工作的评价只看论文数量的弊端，人们谈得很多，也很在理，另一种极端的意见我认为也无益，即认为只有解决了大问题的人才有用，其余全是垃圾，这不利于青年研究工作者树立自己的信心。有一种关于中国古代科举取人的得失的论点，对我有所启发。不少人认为科举考的都是四书五经，这全是教条，从这里选拔不出真正的人才。另一方面反驳这个论点说一个连四书五经都读不通的人与能读通的人是有差距的。历史上也证明了这一点，从

科举中选拔出的人基本上都是读书人中的优秀分子。与此对比，我们现在，鼓励青年人出论文，写出的文章也不一定全是高水平的，但是从不会写到能发表出文章来，他们水平确实是提高了。为了能写出文章，他要付出相当的努力。另外，这些文章也不是一点用都没有。从整个数学的发展看，精品也要在大量的一般性文章的基础上才有产生的土壤，这就好比踢足球，最后一个人踢进球了，其实前边有好几个要为他传球，有时候那一脚看不出什么大用，但可能就是最后进球时不可少的一脚。

在统计学教学方面，这几十年来无论从质量和数量看，都有很大的提高，但也还存在不少问题，在理论教学方面，我个人感到一个问题是教材老化。例如，有关估计和检验的经典理论的材料，在基础课中占了不小的比重，其中有一些内容对目前的理论研究以至应用上，都已用得很少。而对近几十年来发展起来的一些新概念、新理论、新方向，在教材中还少有反映。另外，由于强调研究生取得学位需要在高级别刊物上发表足够数量的论文，使研究生把大部分时间放在一个很窄的领域里，而对统计的全面知之不多，这很不利研究生毕业以后的发展，即我们这里常讲到的“后劲不足”的问题。

Clinical Trials for Drug Development: Some Statistical Problems

By Tze Leung Lai

About two years ago, the editor of the *ICSA Bulletin* invited me to contribute an article giving an overview of my research. I thanked him for the invitation but told him that I did not know how to proceed since during the past thirty years I had been working in various areas of statistics and probability and different fields of application that might be difficult to provide a unified and not too lengthy overview. On the other hand, I asked him if he would agree to the possibility of narrowing the scope of the article to something related to my plenary talk (which was still vague in my mind at that time) in the 2003 ICSA Applied Statistics Symposium (later postponed to 2004 because of SARS), entitled "Current Statistical Issues in Clinical Trials for Drug Development." His answer was enthusiastically positive, and after my talk in June, he reminded me of what I was supposed to send him. The "Statistical Problems" in the title of this article, therefore, are closely related to several "issues" I discussed in that talk. They also reflect some of my research interests during the past decade related to clinical trials for drug development. I have been attracted to them not only because of their practical relevance but also because they are challenging and fundamental statistical problems that have far-reaching implications beyond biopharmaceutics and clinical trials.

1. Efficient group sequential designs and interim analysis of clinical trials

In standard clinical trial designs, the sample size is determined by the power at a given alternative. In practice, however, it is often difficult for investigators to specify a realistic alternative at which sample size determination can be based, especially for new treatments about which there is little information concerning the magnitude of the treatment effect before actual data are collected. Moreover, the choice of the alternative to determine the sample size is usually guided not only by published results on the magnitude of the treatment difference to be expected but also by economic considerations related to funding and duration for the trial and by administrative considerations related to other trials that compete for patients and investigators. Although the protocol of a trial typically justifies its choice of sample size by stating some conventional level, such as 80% or 90%, of power at a plausible alternative, there are actually many other feasibility considerations that are difficult to quantify and much harder to explain than the precise but oversimplified statement of some prescribed power at the alternative.

Group sequential designs that can adapt to information about unknown parameters during interim analyses provide natural ways to address the above difficulty in clinical trial

designs due to lack of information at the design stage. A few years ago, together with Mei-Chiung Shih who had just finished her Ph.D. dissertation at Stanford under my supervision, I undertook the project of developing flexible and efficient group sequential designs that can 'self-tune' to the unknown parameters during the course of the trial, under pre-specified constraints on the maximum sample size and Type I error probability. Previous work on efficient group sequential designs uses the expected sample size at an alternative, or more generally a weighted average of expected sample sizes over a set of parameter values, as the optimization criterion while controlling the error probabilities under the null hypothesis and a specified alternative at prescribed levels; see Pocock (1982), Wang & Tsiatis (1987), Kim & DeMets (1987), Eales & Jennison (1992, 1995) and Barber & Jennison (2002). There are several practical difficulties with this approach to efficient group sequential design. First, even though the mean of the random sample size is minimized at some alternative, the maximum sample size can be substantially larger than the mean and also the fixed sample size. Secondly, the optimization problem requires precise specification of the relative sizes of all groups, e.g. equal group sizes, but it is often not feasible to do so prior to the trial because interim analyses are usually scheduled at calendar times for administrative reasons; see Chapter 7 of Jennison & Turnbull (2000). Thirdly, as pointed out in the preceding paragraph, it may be difficult to come up with a realistic alternative before data are collected from the trial, but the optimization problem depends on the chosen alternative.

Clearly efficiency of a group sequential test depends not only on the design of the stopping rule but also on the test statistics used. To fix the ideas, we began by focusing on the generic special case of a one-parameter exponential family $f_\theta(x) = e^{\theta x - \psi(\theta)}$ of densities with respect to some measure on the real line, and consider the problem of testing the one-sided hypothesis $H_0 : \theta \le \theta_0$ at significance level α and taking no more than M observations $X_1, X_2, \ldots$ Sufficient statistics are the sample means which are maximum likelihood estimators of $\psi'(\theta)$, and the Kullback-Leibler information number is given by

$$I(\theta, \lambda) = E_\theta[\log\{f_\theta(X_i)/f_\lambda(X_i)\}] = (\theta - \lambda)\psi'(\theta) - \{\psi(\theta) - \psi(\lambda)\}. \tag{1}$$

Letting $S_n = X_1 + \ldots + X_n$, the fixed sample size test that rejects H_0 if $S_M \ge c_\alpha$ has maximal power at any alternative $\theta > \theta_0$, in particular at the alternative $\theta(M)$ 'implied' by M (in the sense that M can be derived from the assumption that the above fixed sample test has some prescribed power $1 - \widetilde{\alpha}$ at $\theta(M)$) when one does not have much information on which to base a realistic alternative. Under the constraint of M on the maximum sample size, it is desirable to adapt to the information on the actual θ gathered during the course of the

trial, allowing early stopping at times of interim analysis, so that the test has nearly optimal expected sample size under a wide range of alternatives but with small loss in power from the fixed sample size test.

To achieve these goals in a group sequential test with k groups and group sizes $n_1, n_2 - n_1, \ldots, n_k - n_{k-1}$ so that $n_k = M$, our approach was to make use of the theory of optimal sequential tests, which was relatively complete in the fully sequential framework (Lai, 2001), and to modify it for the group sequential setting. This theory leads to a group sequential test with rejection region of the form $S_{n_k} \geq c$ at the kth analysis, where $c > c_\alpha$ but c does not differ much from c_α. Let $\bar{X}_n = S_n/n$. During the first $k-1$ analyses, the test uses the maximum likelihood estimator $\widehat{\theta}_{n_i} = (\psi')^{-1}(\bar{X}_{n_i})$ to estimate θ and a stopping rule of the form

$$\widehat{\theta}_{n_i} > \theta_0 \text{ and } n_i I(\widehat{\theta}_{n_i}, \theta_0) \geq b, \text{ or} \tag{2a}$$

$$\widehat{\theta}_{n_i} < \theta(M) \text{ and } n_i I(\widehat{\theta}_{n_i}, \theta(M)) \geq \widetilde{b}, \tag{2b}$$

for $1 \leq i \leq k-1$. If (2a) holds, the test rejects H_0 upon stopping. If stopping occurs with (2b), it accepts H_0. The thresholds $b, \widetilde{b}$ and c are so chosen that $P_{\theta_0}(\text{Test rejects } H_0) = \alpha$ and that the power of the test at $\theta(M)$ does not differ much from its upper bound $1 - \widetilde{\alpha}$. A simple way of choosing $b, \widetilde{b}$ and c satisfying these properties is as follows. Let $0 < \epsilon < \frac{1}{2}$ and define $\widetilde{b}$ by the equation

$$P_{\theta(M)}\{\widehat{\theta}_{n_i} < \theta(M) \text{ and } n_i I(\widehat{\theta}_{n_i}, \theta(M)) \geq \widetilde{b} \text{ for some } 1 \leq i \leq k-1\} = \epsilon\widetilde{\alpha}.$$

After determining $\widetilde{b}$, define b and then c by the equations

$$\Sigma_{j=1}^{k-1} P_{\theta_0}\{\widehat{\theta}_{n_j} > \theta_0 \text{ and } n_j I(\widehat{\theta}_{n_j}, \theta_0) \geq b,$$
$$n_i I(\widehat{\theta}_{n_i}, \theta_0) 1_{\{\hat{\theta}_{n_i} > \theta_0\}} < b \text{ and } n_i I(\widehat{\theta}_{n_i}, \theta(M)) 1_{\{\hat{\theta}_{n_i} < \theta(M)\}} < \tilde{b} \text{ for } i < j\} = \epsilon\alpha,$$

$$P_{\theta_0}\{S_{n_k} \geq c,\ n_i I(\widehat{\theta}_{n_i}, \theta_0) 1_{\{\hat{\theta}_{n_i} > \theta_0\}} < b \text{ and } n_i I(\widehat{\theta}_{n_i}, \theta(M)) 1_{\{\hat{\theta}_{n_i} < \theta(M)\}} < \widetilde{b} \text{ for } i < k\}$$
$$= (1 - \epsilon)\alpha.$$

Note that although the rejection region in favor of the treatment at each of the k times is one-sided, involving the thresholds b and c, there is also a "futility" boundary in (2b) with threshold $\widetilde{b}$ that stops the trial when it becomes unlikely to demonstrate efficacy of the treatment within the resources allocated to the trial. We call these tests the *modified Haybittle-Peto tests* as they use a more flexible choice of b than $|S_{n_i}|/\sqrt{n_i} \geq 3\sigma$ for $1 \leq i \leq k-1$ in the group sequential test proposed by Haybittle (1971) and Peto *et al.* for normally distributed X_i.

Noting that the $n_j I(\widehat{\theta}_{n_j}, \theta_*)$ used in the stopping rule (2) are generalized likelihood rates (GLR) statistics for testing $\theta = \theta_*$, we then extended these group sequential tests to the multiparameter exponential family and to multi-armed clinical trials by using appropriate GLR statistics in these problems. The basic idea behind the proposed class of tests, therefore, is to estimate the unknown parameter θ by maximum likelihood during the course of the trial and to use it to replace θ in an approximately optimal sequential test that assumes known θ. These group sequential tests, which are shown in our recent paper (Lai & Shih, 2004) to have nearly optimal power and expected sample size properties over a wide range of alternatives, do not require pre-specification of the group sizes, nor do they require estimation of the "maximum information" of the trial in the error-spending approach (see Chapter 7 of Jennison & Turnbull (2000)). They are, therefore, very flexible and can be easily extended to more complex settings. An important extension is related to the design and interim analysis of clinical trials for comparing the failure times between two treatment groups; see Gu & Lai (1991, 1998). A general weak convergence theory for certain time-sequential censored rank statistics under the null hypothesis of no treatment difference and under local alternatives has been developed, showing that these time-sequential statistics behave asymptotically like cumulative sums of independent normal random variables, with the number of summands up to time t_j known only at the calendar time t_j of the jth interim analysis. This is a consequence of the independent increments property of the limiting Gaussian process, whose increments have variances that are not specified in advance but have to be estimated from the data. Despite such complexity, the modified Haybittle-Peto tests can be easily modified to develop efficient time-sequential tests subject to prescribed constraints on the type I error probability and maximum study duration, in contrast with the error-spending approach that uses simulations at each interim analysis to estimate the maximum information under the null hypothesis; see Scharfstein & Tsiatis (1998).

Although group sequential designs are attractive because they allow for early termination while preserving the overall significance level of the test and can adapt to information gathered during the course of the trial, they may also introduce substantial bias when one applies standard point and interval estimates for the parameters of interest following the test, and this potential bias has inhibited the use of group sequential methodology. After reviewing previous work in this area, I began a systematic investigation of the problem of constructing valid confidence intervals following group sequential tests in the mid-nineties. Siegmund's (1978) seminal paper introduced an exact method, based on ordering the sample space in a certain way, to construct exact confidence intervals for the mean of a normal

population with known variance following a repeated significance test. Tsiatis, Rosner & Mehta (1984) extended Siegmund's method to the group sequential tests of Pocock (1977) and O'Brien & Fleming (1979). Alternative orderings of the sample space were subsequently introduced by Chang & O'Brien (1986), Rosner & Tsiatis (1988), Chang (1989) and Emerson & Fleming (1990). For samples of fixed size, an important methodology for constructing confidence intervals without distributional assumptions is Efron's (1987) bootstrap method. This prompted me to try resampling methods to adjust for the bias due to the possibility of early stopping. In Chuang & Lai (1998), we studied bootstrap confidence intervals for a population mean in a group sequential setting as an alternative to the exact methods. We found that, since the stopping rule makes the approximate pivots in nonsequential bootstrap methods highly "non-pivotal", the bootstrap method does not yield reliable confidence intervals in a group sequential setting. However, by integrating the main ideas behind the exact and bootstrap methods, we were able to develop a resampling method for the construction, after a group sequential test, of confidence intervals whose coverage probabilities are nearly equal to the nominal ones.

This hybrid resampling approach was subsequently developed further in Chuang & Lai (2000), where we showed that it also works well in other situations where the bootstrap method fails. For group sequential tests, the hybrid resampling approach in Chuang & Lai (1998, 2000) assumes the group sizes to be pre-determined constants. To extend the approach to random group sizes, Wenshi Li and I recently found that the ordering method introduced by Siegmund (1978) still works in the case of sample means. To begin with, suppose $Z_1, Z_2, \ldots$ are i.i.d. normal random variables with known variance 1 and unknown mean μ and T is a two-sided stopping rule of the form $T = \inf\{n \in J : S_n \geq b_n \text{ or } S_n \leq a_n\}$, where $S_n = Z_1 + \ldots + Z_n$ and J is a finite set of positive integers. Siegmund (1978) orders the sample space of (T, S_T) as follows: $(t,s) > (t',s')$ whenever (i) $t = t'$ and $s > s'$, or (ii) $t < t'$ and $s \geq b_t$, or (iii) $t > t'$ and $s' \leq a_{t'}$. Let μ_c denote the value of μ for which $P_\mu\{(T, S_T) \geq (t,s)_{obs}\} = c$, where $(t,s)_{obs}$ denotes the observed value of (T, S_T). Siegmund's confidence interval is $\mu_\alpha \leq \mu \leq \mu_{1-\alpha}$, which has coverage probability $1 - 2\alpha$. Note that this ordering only involves considering possible sample paths that stop (or do not stop if downcrossing of the lower boundary is observed) prior to the observed stopping time. Hence a hybrid resampling version that removes the assumption of normality in Siegmund's method does not require one to generate data beyond the observed stopping time t; see Chuang & Lai (1998) for details and the second-order accuracy of the method. Although the set J considered by Siegmund (1978) is nonrandom, the argument of Chuang & Lai (1998) is still

applicable to the case of random $J = \{n_1, \ldots, n_k\}$ by conditioning on $(n_1, \ldots, n_k)$, thereby establishing the second-order accuracy of the hybrid resampling method when the random vector $(n_1, \ldots, n_k)$ is independent of $\{Z_i, i \geq 1\}$. The main motivation behind my work with Li was the construction of confidence intervals for survival parameters in time-sequential clinical trials with survival endpoints, which will be described below.

Suppose that a clinical trial to compare times to failure between two treatment groups X and Y involves n patients who enter the trial serially, are randomly assigned to treatment X or Y and are then followed until they fail or withdraw from the study or until the study is terminated. Let $T_i' \geq 0$ denote the entry time and $X_i > 0$ the survival time (or time to failure) after entry of the ith subject in treatment group X, and let T_j'' and Y_j denote the entry time and survival time after entry of the jth subject in treatment group Y. Thus the data at calendar time t consist of $(X_i(t), \delta_i'(t)), i = 1, \ldots, n'$, and $(Y_j(t), \delta_j''(t)), j = 1, \ldots, n''$, where $X_i(t) = X_i \wedge \xi_i' \wedge (t - T_i')^+, Y_j(t) = Y_j \wedge \xi_j'' \wedge (t - T_j'')^+$, $\delta_i'(t) = I_{\{X_i(t) = X_i\}}, \delta_j''(t) = I_{\{Y_j(t) = Y_j\}}$, $m_{n,t}'(s) = \sum_{i=1}^{n'} I_{\{X_i(t) \geq s\}}$, $m_{n,t}''(s) = \sum_{j=1}^{n''} I_{\{Y_j(t) \geq s\}}$, and $\xi_i'(\xi_j'')$ denotes the withdrawal time, possibly infinite, of the ith (jth) subject in treatment group $X(Y)$. At a given calendar time t, one can compute, on the basis of the observed data from the two treatment groups, a rank statistic of the general form considered by Tsiatis (1982):

$$S_n(t) = \sum_{i=1}^{n'} \delta_i'(t) Q_n(t, X_i(t)) \left\{ 1 - \frac{m_{n,t}'(X_i(t))}{m_{n,t}'(X_i(t)) + m_{n,t}''(X_i(t))} \right\}$$

$$- \sum_{j=1}^{n''} \delta_j''(t) Q_n(t, Y_j(t)) \frac{m_{n,t}'(Y_j(t))}{m_{n,t}'(Y_j(t)) + m_{n,t}''(Y_j(t))}, \tag{3}$$

where $Q_n(t,s)$ is some weight function satisfying certain measurability assumptions. The case $Q_n \equiv 1$ corresponds to the logrank statistic. Let $H_{n,t}$ denote a product-limit-type estimator of the common distribution function of the two treatment groups under the null hypothesis, based on $\{(X_i(t), \delta_i(t), Y_j(t), \delta_j(t)) : i \leq n', j \leq n''\}$. For a general weight function of the form $Q_n(t,s) = \psi(H_{n,t}(s))$ in (3), Minggao Gu and I have shown that $\{S_n(t)/\sqrt{n}, t \geq 0\}$ converges weakly to a Gaussian process with independent increments and variance function $V(t)$ under the null hypothesis, and contiguous alternatives. Note that $V(t)$ is called the "information time" by Lan & DeMets (1989). The mean function of the limiting Gaussian process is 0 under the null hypothesis and is of the form $\mu_g(t)$ under contiguous alternatives that satisfy

$$\int_0^{t^*} |\frac{d\Lambda_G}{d\Lambda_F} - 1| d\Lambda_F = O(\frac{1}{\sqrt{n}}), \ \sqrt{n}\{\frac{d\Lambda_G}{d\Lambda_F}(s) - 1\} \to g(s)$$

as $n \to \infty$, uniformly over closed subintervals of $\{s \in [0, t^*] : F(s) < 1\}$, where Λ_F and Λ_G are the cumulative hazard functions of F and G; see Gu & Lai (1991), in which we have also provided consistent estimates $V_n(t)$ of $V(t)$ and shown that $\mu_g(t) = V(t)$ in the case of asymptotically optimal score functions $\psi(\cdot) = g(F^{-1}(\cdot))$. In practice, the actual alternatives are unknown and μ_g need not even be monotone when ψ is not optimal for the actual alternatives, such as using logrank statistics for non-proportional hazards alternatives, for which we have shown in Gu & Lai (1998) that time-sequential tests based on $S_n(t)$ can achieve *both* savings in study duration and increase in power over the fixed-duration test based on $S_n(t^*)$. It is widely recognized that tests of treatment effects based on the rank statistics (3) may lose substantial power when the effects of other covariates are strong. In nonsequential trials, a commonly used method to remedy this when logrank statistics are used is to assume the proportional hazards regression model and to use Cox's partial likelihood approach to adjust for other covariates. Tsiatis, Rosner & Tritchler (1985), Gu & Ying (1995) and Bilias, Gu & Ying (1997) have developed group sequential tests using this approach. Instead of relying on the proportional hazards model to adjust for concomitant variables, it is useful to have other methods for covariate adjustment, especially in situations where other score functions than the logrank are used in (3) to allow for the possibility of non-proportional hazards alternatives. Lin (1992) and Gu & Lai (1998) have proposed alternative covariate adjustment methods based on rank estimators and M-estimators in accelerated failure time models.

The recent work of Lai & Shih (2004) showing the efficiency of modified Haybittle-Peto tests relative to the error spending approach suggests that one can focus on the modified Haybittle-Peto-type boundary in constructing a time-sequential test based on (3), with t restricted to the set $\{t_1, \ldots, t_k(= t^*)\}$ of calendar times at which interim analyses are conducted, since it yields a statistically efficient stopping rule that can also circumvent the difficulty of "calendar time" versus "information time". The Monte Carlo simulation method provides a flexible and practical way to compute power and expected duration of these complex trials, and also to check the adequacy of the normal approximation to the type I error probability under various scenarios of baseline survival, censoring pattern, noncompliance, and accrual rate. To provide the clinical trial designer with a tool to perform these Monte Carlo simulations, Gu & Lai (1999) developed a simulation program which gives the user some options for choosing the stopping boundary, including the modified Haybittle-Peto-type boundary. The program also allows the user to choose the score function ψ in $Q_n(t, s) = \psi(H_{n,t}(s))$ from a general family proposed by Self (1991). It enables the clinical

trialist, who can download it from a website listed in the paper, to select the test statistic most sensitive to the anticipated kind of departures from the null hypothesis. Gu & Lai (1999) also incorporated this power calculation program into another program that computes the sample size of a group sequential trial having a prescribed power at given baseline and alternative distributions.

The above software only has the design module, but its basic programs can be modified for the development of an analysis module that can be used for interim analysis of clinical trials data. I am currently working with my Ph.D. student Zheng Su from the Department of Computer Science at Stanford to develop an analysis module that will also include software for terminal analysis of the trial. Concerning such terminal analysis, some progress towards constructing valid confidence intervals following time-sequential tests was recently made in Lai & Li (2004). Consider the logrank statistic (3) with $Q_n \equiv 1$ and a group sequential test of $H_0 : F = G$ with stopping rule of the form $\tau = \min\{t_j : |S_n(t_j)| \geq b_j V_n^{1/2}(t_j)\}$, where $t_1 < \ldots < t_k$ denote the calendar times of interim analysis and $V_n(t)$ is either Mantel's (1966) estimate of the null variance of $S_n(t)$ or (total number of deaths up to time t)/4. Assuming the proportional hazards model $\Lambda_F = \theta\Lambda_G$, the null hypothesis can be rephrased as $H_0 : \theta = 1$, where θ is the hazard ratio. Let P_β denote the probability measure under which $\theta = e^\beta$. Thus, β is the regression parameter in Cox's hazard regression model with covariate that takes the value 1 (under F, representing treatment) or 0 (under G, representing control), for which $S_n(t)$ is the efficient score statistic. For small β (such that $\sqrt{n}\,\beta \to \mu$), $\{(S_n(t_j)/\sqrt{n}, V_n(t_j)/n) : 1 \leq j \leq K\}$ converges in distribution to $\{(W(V(t_j)), V(t_j)) : 1 \leq j \leq K\}$, where $W(\cdot)$ is a Wiener process with drift coefficient μ. Analogy with the case of normal means and random group sizes described above in connection with hybrid resampling led us to the following ordering of the sample space, which reduces to Siegmund's (1978) ordering in the case of confidence intervals for means. Let $\Psi_t = S_n(t)/V_n(t)$. Order the sample space of (τ, Ψ_τ) by:

$$(\tau_1, \Psi^{(1)}_{\tau_1}) \leq (\tau_2, \Psi^{(2)}_{\tau_2}) \quad \text{if and only if} \quad \Psi^{(1)}_{\tau_1 \wedge \tau_2} \leq \Psi^{(2)}_{\tau_1 \wedge \tau_2}. \tag{4}$$

Similar to the normal mean case, let $p(\beta) = P_\beta\{(\tau, \Psi_\tau) > (\tau, \Psi_\tau)_{\text{obs}}\}$. Then $\{\beta : \alpha < p(\beta) < 1 - \alpha\}$ is a confidence set for β with coverage probability $1 - 2\alpha$. Even if the baseline distribution G should the known, the probability $p(\beta)$ has to be evaluated by simulation. In practice G is unknown and we can replace it by Breslow's estimate $\widehat{G}$ from all the data at the end of the trial. This suggests replacing $p(\beta)$ by

$$\widehat{p}(\beta) = P\{(\tau^{(\beta)}, \Psi^{(\beta)}_{\tau^{(\beta)}}) > (\tau, \Psi_\tau)_{\text{obs}}\}, \tag{5}$$

where the superscript (β) means that the observations are generated by hybrid resampling from the baseline distribution $\widehat{G}$, with β as the hazard ratio. Since $\widehat{p}(\beta)$ is an increasing function of β, the confidence set $\{\beta : \alpha < \widehat{p}(\beta) < 1-\alpha\}$ with coverage probability $1-2\alpha+O(n^{-1})$ becomes an interval whose endpoints $\underline{\beta} < \bar{\beta}$ are defined by $\widehat{p}(\underline{\beta}) = \alpha$, $\widehat{p}(\bar{\beta}) = 1-\alpha$. Details are given in Lai & Li (2004), where simulation studies and analytic results show that the confidence intervals thus constructed have coverage probabilities close to nominal values. Zheng Su and I are currently working on extensions of this approach to other (non-proportional hazards) survival models and other test statistics. We are also developing more efficient simulation procedures based on importance sampling and resampling to speed up the computation of (5) by Monte Carlo.

2. Population PK/PD and nonlinear mixed effects models

Pharmacology is the science dealing with interactions between living systems and molecules, especially chemicals introduced from outside the system. The component of a cell or organism that interacts with a drug and initiates a chain of biochemical events leading to the drug's therapeutic and toxic effects is called a *receptor*. The receptor concept has become the central focus of investigation of *pharmacodynamics* (PD) – the study of drug effects and their mechanisms of action. How a drug dose produces its effects involves not only PD but also *pharmacokinetics* (PK), which is concerned with the concentration-time curve associated with the absorption, distribution and elimination phases of a single administration of the drug. In Lai, Shih & Zhu (2003), we have given an overview of the basic principles, models and statistical methods in PK/PD and of their roles in drug development. In many PK/PD studies, data are collected from a number of subjects, some of whom may have intensive blood sampling while others only have sparse data. A primary objective of these studies is to study the PK/PD characteristics of the entire population, such as how they vary with certain covariates. This requires a population model, and nonlinear mixed effects modeling provides a valuable tool to address this problem.

Since the seminal work of Sheiner & Beal (1980), nonlinear mixed effects models of the form

$$y_{ij} = f_i(t_{ij}, \theta_i) + \varepsilon_{ij}, \quad \theta_i = g(x_i, \beta) + b_i \quad (1 \le j \le n_i,\ 1 \le i \le I), \tag{6}$$

have become widely used in population PK/PD. In (6), θ_i is a $1 \times r$ vector of the ith subject's parameters whose regression function on the subject's observed covariate x_i is $g(x_i, \beta)$ with a $1 \times s$ parameter vector β, which is the "fixed effect" to be estimated. The "random effects" b_i in (6) are assumed to be i.i.d. and their nonzero components have a common distribution G with mean 0. The ith subject's response y_{ij} at t_{ij} has mean $f_i(t_{ij}, \theta_i)$, in which f_i is a known

function. Given θ_i, the random errors ε_{ij} are assumed to be independent normal random variables with mean 0 and standard deviation $\sigma\omega_{ij}(\theta_i)$, in which ω_{ij} is a given function and σ is an unknown parameter. In PK, the concentrations at times t_{ij} after the administration of a single dose D_i are often modeled by the one-compartment model

$$y_{ij} = \frac{D_i k_i \tilde{k}_i}{Cl_i(k_i - \tilde{k}_i)}(e^{-\tilde{k}_i t_{ij}} - e^{-k_i t_{ij}}) + \varepsilon_{ij}, \quad 1 \le j \le n_i. \tag{7}$$

Here $Cl_i, k_i, \tilde{k}_i$ are the ith subject's total body clearance, absorption rate, and elimination rate, respectively, and their logarithms constitute the vector θ_i in (6). The regression function g relates θ_i to the ith subject's physiologic characteristics that constitute the covariate vector x_i. The population distribution G is usually assumed to be normal with unknown parameters which, together with β and σ, can be estimated by maximum likelihood. Unlike linear mixed effects models in which the normality assumption on G yields closed-form expressions of the likelihood, the normality of G in nonlinear mixed effects models leads to computationally intensive likelihoods that involve I multiple integrals. A commonly used approach, as adopted in the software package NONMEM (Beal & Sheiner, 1992), and the `nlme` procedure in S-Plus due to Lindstrom & Bates (1990), is to develop iterative schemes based on first-order approximations of $f_i(t_{ij}, g(x_i, \beta) + b_i)$ in (6), so that the normality assumption on G can be used to reduce the problem to that of a linear Gaussian mixed effects model at each iterative step.

A basic issue with this approximation is that when some of the subjects have sparse data there are considerable errors in approximating the likelihood function via these first-order approximations, as noted by Yafune et al. (1998) who propose to use Monte Carlo integration to evaluate the I multiple integrals in the likelihood function for Phase 1 studies but point out that the computational time (already taking 22 hours in their particular Phase 1 trial) may be too long for Phase 2 (or later) trials to be of practical interest. Another issue is that the actual population distribution may be highly nonnormal. Since there is no computational advantage in using normal G when first-order approximations to reduce to linear Gaussian mixed effects models are not used, it may be more appropriate to try more flexible parametric families for G. Davidian & Gallant (1992), Fattinger, Sheiner & Verotta (1995) and Magder & Zeger (1996) have proposed certain parametric families that incorporate skewness and multimodality, but they are too computationally intensive for routine use.

In Lai & Shih (2003b) and Lai, Shih & Wong (2004a), we address these issues by developing a "hybrid" approach that uses first-order approximations based on Laplace's

method to evaluate the likelihood when the subject has sufficient data, in combination with Monte Carlo approximations of the likelihood involving relatively few simulation runs when the subject has sparse data. To begin with, suppose the distribution G is normal with mean 0 and covariance matrix Σ. For given values of β, σ and Σ, the integral for the ith subject in the likelihood function can be written as an expectation $E\psi_i(b)$, which can be computed by Monte Carlo simulations of the random vector b with the normal density function ϕ_Σ having mean 0 and covariance matrix Σ. Alternatively, letting $e^{\ell_i(b)} = \psi_i(b)\phi_\Sigma(b)$, we can use Laplace's method to approximate the integral

$$\int \cdots \int e^{\ell_i(b)} db^{(1)} \ldots db^{(r)} \doteq (2\pi)^{r/2} \, |-\ddot{\ell}_i(\widehat{b}_i)|^{-1/2} e^{\ell_i(\widehat{b}_i)}, \tag{8}$$

where $\ddot{\ell}_i$ is the Hessian matrix of second partial derivatives of ℓ_i with respect to the components $b^{(j)}$ of b, and $\widehat{b}_i$ is the maximizer of $\ell_i(b)$. Laplace's approximation basically approximates ℓ_i by a quadratic function in a neighborhood of the maximizer $\widehat{b}_i$ as $\lambda_{\min}(-\ddot{\ell}_i(\widehat{b}_i)) \to \infty$, where $\lambda_{\min}(\cdot)$ denotes the minimum eigenvalue of a symmetric matrix. If the observations (y_{ij}, t_{ij}), $1 \le j \le n_i$, are sufficiently informative about the ith subject's parameter vector $\theta_i = g(x_i, \beta_0) + b_i$, then for (β, σ) near the true value (β_0, σ_0), $\ell_i(b)$ becomes peaked around $\widehat{b}_i$ and can be well approximated by the quadratic function $\ell_i(\widehat{b}_i) + (b - \widehat{b}_i)^T \ddot{\ell}_i(\widehat{b}_i)(b - \widehat{b}_i)/2$. Laplace's approximation is also applicable when $\lambda_{\min}(\Sigma^{-1})$ is large, which occurs when the distribution of b is concentrated around 0.

When $\lambda_{\min}(\Sigma^{-1})$ is not sufficiently large and the ith subject has sparse data, Laplace's method may give a poor approximation to the left hand side of (8), which will be denoted by $L_i(\beta, \sigma, \Sigma)$. These considerations led to the following hybrid method in Lai & Shih (2003b) for evaluating $L_i(\beta, \sigma, \Sigma)$, which combines Laplace's with the Monte Carlo approximation. Choose a threshold c and let $V_i = -\ddot{\ell}_i(\widehat{b}_i)$.

(i) If $\lambda_{\min}(V_i) < c$, evaluate $L_i(\beta_i, \sigma, \Sigma)$ by the Monte Carlo approximation $B^{-1} \sum_{j=1}^{B} \psi_i(\Sigma^{1/2} z_j)$, where z_j, $j = 1, \ldots, B$, are independent random vectors from the standard normal distribution. Note that $\Sigma^{1/2} z_j$ is normal with mean 0 and covariance matrix Σ.

(ii) If $\lambda_{\min}(V_i) \ge c$, evaluate $L_i(\beta, \sigma, \Sigma)$ by its Laplace approximation $(2\pi)^{r/2} \, |V_i|^{-1/2} e^{\ell_i(\widehat{b}_i)}$.

By performing simple diagnostics on the appropriateness of using Laplace's approximation to evaluate the integral in (8) for the ith subject, the hybrid approach preserves the computational simplicity of Laplace's method when it can be used and switches to the Monte Carlo method when Laplace's method fails. If the ith subject has enough data so that $\ell_i(b)$ is peaked around $\widehat{b}_i$ for (β, σ) near (β_0, σ_0), the Monte Carlo approach becomes unreliable

unless B is very large or importance sampling is used to generate the B samples from a distribution that is peaked around $\widehat{b}_i$, so Laplace's method gives a better approximation to $L_i(\beta, \sigma, \Sigma)$ in this case. On the other hand, if the ith subject has sparse data and $\ell_i(b)$ is relatively flat in b, then applying the Monte Carlo approach is tantamount to choosing a random distribution G_i, which is the empirical distribution of a sample of B random vectors $\Sigma^{1/2} z_j$ with standard normal z_j, to approximate G. As there is no need for "high resolution" in the random distribution used to approximate the actual G (which may not even be normal), using $50 \le B \le 200$ samples in the Monte Carlo method should be able to provide enough statistical detail while maintaining a low computational cost comparable to that of the first-order method that can be derived from Laplace's approximation.

In Lai, Shih & Wong (2004a), we improve the Monte Carlo method in (i) above by using importance sampling instead of sampling directly from ϕ_Σ. Specifically, we evaluate $L_i(\beta, \sigma, \Sigma)$ by the importance sampling estimate

$$\sum_{j=1}^{B} \psi_i(\zeta_j) w_j \Big/ \sum_{j=1}^{B} w_j, \tag{9}$$

where $P\{\zeta_j = \Sigma^{1/2} z_j\} = p = 1 - P\{\zeta_j = \hat{b}_i + (V_i + \epsilon I)^{-1/2} z_j\}$ with standard normal z_j, which corresponds to sampling ζ_j from a mixture of the prior normal distribution with density ϕ_Σ and the posterior normal distribution with mean $\hat{b}_i$ and covariance matrix $(V_i + \epsilon I)^{-1}$, choosing some small $\epsilon > 0$ to ensure that the covariance matrix is invertible. Denoting the density function of this mixture distribution by λ, note that $\lambda(x) = p\phi_\Sigma(x) + (1 - p)\phi_{(V_i + \epsilon I)^{-1}}(x - \hat{b}_i)$. The w_j in (9) are the importance weights given by $w_j = \phi_\Sigma(\zeta_j)/\lambda(\zeta_j)$. Note that the special case $p = 1$ reduces to direct Monte Carlo in (i) above, whereas the case $p = 0$ corresponds to a Monte Carlo implementation of Laplace's method, and recommend choosing p in the range $0.2 \le p \le 0.5$.

Following Lindstrom & Bates (1990), the iterative procedure used to maximize the logarithm of $\prod_{i=1}^{I} L_i(\beta, \sigma, \Sigma)$ first maximizes over β for fixed $\eta = (\sigma, \Sigma)$ and then maximizes over η for fixed β, repeating until convergence or until a prespecified maximum number of iterative steps is reached. To avoid numerical instability in differentiating $\log L_i$ with respect to β, care should be taken when L_i computed by (9) is small, in which case we can circumvent the difficulty by simply replacing L_i by its Laplace approximation whose logarithm is convenient for differentiation. Details on the choice of the threshold c and starting values for β, σ, Σ can be found in Section 3.2 of Lai & Shih (2003b). In particular, for typical population PK studies that involve both healthy volunteers from whom intensive

blood sampling is conducted and clinical patients who only have sparse blood samples, one can first single out "potentially good" studies and check their $\lambda_{\min}(V_i)$ values. It is usually adequate to choose a threshold c as low as 10 for $\lambda_{\min}(V_i)$ to determine if these potentially good studies indeed qualify for using Laplace's approximation to $L_i(\beta, \sigma, \Sigma)$. Moreover, for such experimental designs, good starting values can be obtained by using only those studies that have sufficient data so that their θ_i can be well estimated by the nonlinear least squares estimate based on (y_{ij}, t_{ij}), $1 \le j \le n_i$.

In the case where the I studies contain many good ones (in the preceding sense), our companion paper Lai & Shih (2003a) has developed nonparametric maximum likelihood estimates of G, β and σ. Previous work in this direction by Mallet (1986, 1992) and Mentré & Mallet (1994) assumes that the x_i are i.i.d. so that β can be estimated via the joint distribution of (x_i, b_i). By using the good studies to initialize the nonparametric maximum likelihood estimate of (G, β, σ),we remove in Lai & Shih (2003a) the restrictive assumption that x_i be i.i.d. and to estimate the finite-dimensional parameter β directly without going through the much more difficult infinite-dimensional problem of estimating the joint distribution of (x_i, b_i). A major finding of Lai & Shih (2003a), however, is that even when G is highly non-normal (e.g., has a bimodal distribution), the parametric estimates of β and σ that assume normal G compare favorably with the nonparametric estimates. An asymptotic theory explaining this is given in Lai & Shih (2003b). . Since the nonparametric maximum likelihood estimate $\widehat{G}$ has relatively low resolution (with very slow rate of convergence to G as the total sample size $n_1 + \ldots + n_I$ becomes infinite), approximating the population distribution G by a normal distribution (with covariance matrix to be estimated from the data), or by the random distribution G_i when $\ell_i(b)$ is relatively flat in the hybrid method, is usually an innocuous assumption in population PK/PD models.

Laplace's asymptotic formula (8) was also used by Breslow & Clayton (1993) and Lee & Nelder (1996) to derive their estimators for generalized linear models, and by Lin & Zhang (1999) in their extension of generalized linear to generalized additive mixed models. Since Laplace's approximation may be inappropriate for individuals with sparse longitudinal observations, we have recently developed in Lai, Shih & Wong (2004b) a hybrid estimation scheme that combines Laplace's approximation with Monte Carlo computations. Moreover, instead of generalized linear or additive models, our approach uses univariate regression splines and their tensor products as basis functions. Not only can these basis functions model the covariate effects and their interactions effectively, but they also involve linear parameters that can be estimated by the same procedure for generalized linear mixed models

once the knots are specified. Using this hybrid method to compute the likelihood function, we have developed likelihood-based inference and model selection schemes that can be used to determine the smoothing parameter (e.g., the number of knots for regression splines) and variables to be included in the regression model.

3. Other topics and concluding remarks

A topic that has attracted much recent interest in pharmaceutical biostatistics is mid-course adaptive designs of clinical trials; see e.g. the Controversial Statistical Issue of the *ICSA Bulletin* (Jan. 2003, pp. 37-51). In estimating the sample size of a controlled clinical trial testing a new drug, one often faces such difficulties as that the published information about the control drug may be unreliable because the dosing methods may have changed, or that new technology has been introduced in the measurements, or that new criteria are used to assess efficacy. Therefore, the problem of sample size re-estimation based on an observed treatment difference at some time before the prescheduled end of the trial has attracted considerable attention during the past decade; see e.g. Gould & Shih (1992), Herson & Wittes (1993), Bauer & Köhne (1994), Proschan & Hunsberger (1995), Wassmer (1998) and Jennison & Turnbull (2000, §14.2). Moreover, there are concerns from the regulatory perspective regarding possible inflation of the type I error probability when such sample size adjustments are used in pharmaceutical trials; see O'Neill (1995). For normally distributed outcome variables with common known variance, Fisher (1998), Cui, Hung & Wang (1999), Lehmacher & Wassmer (1999), Posch & Bauer (1999) and Shen & Fisher (1999) have proposed ways to adjust the test statistics after mid-course sample size modification so that the type I error probability is maintained at the prescribed level. Jennison & Turnbull (2003) recently gave a general form of these methods and showed that they performed considerably worse than group sequential tests. Tsiatis & Mehta (2003) independently came to the same conclusion, pointing out their inefficiency because the adjusted test statistics are not functions of the sufficient statistic (T, S_T).

It is possible to adhere to efficient generalized likelihood ratio statistics in a mid-course adaptive design if one uses the non-normal (due to the mid-course adaptation) sampling distribution of the test statistic instead of ignoring the nonnormality and thereby resulting in type I error inflation. I am currently working on a resampling method for testing and interval estimation in mid-course adaptive designs. Besides using efficient test statistics, other statistical issues need to be addressed to make the current generation of adaptive designs more efficient. In particular, there is uncertainty in the mid-course parameter estimates that

determine the final sample size of the adaptive design, and the uncertainty depends on the choice of the initial sample size. This problem was already recognized in Simon's (1989) seminal paper on optimal two-stage designs for testing $H_0 : p \leq p_0$, in which p is the success probability of a treatment and the optimization problem is to choose the initial sample size so that the expected sample size under p_0 is minimized subject to prescribed type I and type II error probabilities at the simple null hypothesis p_0 and a given alternative p_1 ($> p_0$). Therefore, besides using efficient test statistics, the efficiency of mid-course adaptive designs depends also on when and how to carry out mid-course adaptation, and sequential testing theory, which has provided us with important clues in the development of efficient group sequential designs, should provide useful insights into this problem. The increasing complexity of medical treatments and the lack of *a priori* knowledge about the treatment effects on different outcome variables have often made it difficult to come up with which endpoints, or which functions thereof, should be included, and which of two or more competing treatment regimens should be used for confirmatory testing of a new drug. Since the maximum resource allocation to a Phase III trial being designed typically depends on what can be claimed in labeling the drug, it is sometimes difficult for a pharmaceutical company to commit a large budget to the trial being planned in the midst of too many uncertainties, so the maximum sample size for a group sequential design may be difficult to pinpoint at the design stage. In this case, which is clearly much more complicated than the oversimplified prototype of a single normally distributed outcome variable with known variance in the literature on the subject, an adaptive design, which finalizes certain design features like maximum sample size, endpoints to be included and treatment regimen to be used after observing an initial sample, is particularly appealing.

Clinical trials are sometimes conducted to compare the efficacy and toxicity of two drugs. Moreover, efficacy is often measured by more than one response variable and so is toxicity. Although univariate methods for assessing each response variable individually have been widely used in this setting, there is often additional need for a single, overall comparison. Combining the univariate comparison by Bonferroni's inequality ignores the correlations between the response variables and may lack power for alternatives at which the response variables are strongly correlated. Beginning with O'Brien's (1984) seminal paper, the problem of comparing multivariate treatment effects has received much attention in the literature, and various fixed sample size and group sequential tests have been developed; see e.g. Pocock, Geller & Tsiatis (1987), Tang, Gnecco & Geller (1989), Laska, Tang & Meisner (1992), Jennison & Turnbull (1993), Tang, Geller & Pocock (1993), Follman (1993) and

Thall & Cheng (1999). These methods are mostly based on the multivariate normal distribution and involve linear combinations or maxima of the response variables. In Bloch, Lai & Tubert-Bitter (2001), we have introduced a new formulation of the multiple endpoint problem in clinical trials to compare two treatments based on their sample means and covariance matrices, incorporating the essential univariate and multivariate features of the treatment effects to be compared. An important ingredient of our approach is to demonstrate that the new treatment is non-inferior to the active control for all endpoints and is superior for some endpoint. We are currently working on extensions of this approach to incorporate different outcome variables, including discrete or continuous immediate response variables and censored survival times, and to accommodate nonlinear and nonparametric tests statistics. The increasing complexity of medical therapies and the technological advances in obtaining a wide variety of measurements from study subjects have made multiple endpoints and adjustments for multiple testing increasingly important issues in the design and analysis of clinical trials. Whereas it is now relatively easy to observe many outcome variables from each subject, it is still difficult to recruit a large enough number of subjects so that the trial has reasonable power for demonstrating that the new treatment is better than the active control even for a single outcome variable. Controlling the overall type I error for multiplicity of testing all outcome variables often leads to an unaffordable sample size for a clinical trial to achieve reasonable power. Moreover, there are also technical difficulties in achieving tight control of the overall type I error probability because the correlations of the p-values of the individual tests are difficult to model realistically and to incorporate into the overall significance level, so conservative Bonferroni bounds are often used instead. This is the motivation behind our approach introduced in Lai, Bloch & Tubert-Bitter (2001).

Closely related to the problem of toxicity and efficacy endpoints in Phase III studies is the design and analysis of Phase I studies to determine the dose and dosing regimen. In typical Phase I studies in the development of relatively benign drugs, the drug is initiated at low doses and slowly escalated to show safety at a level where some positive response occurs, and healthy volunteers are used as study subjects. This paradigm does not work for diseases like cancer, for which a non-negligible probability of severe toxic reaction has to be accepted to give the patient some chance of a favorable response to the treatment. Moreover, in many such situations, the benefits of a new therapy may not be known for a long time (perhaps years) after enrollment but toxicities manifest themselves in a relatively short time period (days or weeks). Therefore patients are used as study subjects, and given the hoped-for (rather than observed) benefit for them, one aims at an acceptable level of toxic response in

determining the dose. Due to the absence of a comprehensive methodology, a number of *ad hoc* protocols for Phase I trials involving new cancer treatments are commonly used. Storer (1989) gives a review of such designs for estimating the maximum tolerated dose (MTD) that he defines to be the dose at which there is 1/3 probability of experiencing a toxic event in connection with a commonly used dose escalation design. The design, which is sequential in nature, treats groups of 3 patients sequentially, starting with the smallest of an ordered set of doses. Escalation occurs if no toxicity is observed in all three patients; otherwise an additional 3 patients are treated at the same dose level. If only one of the 6 patients has toxicity, escalation again continues; otherwise the trial stops with the current dose declared as the MTD. As pointed out by Storer (1989), these designs are difficult to analyze since even a strict quantitative definition of MTD is lacking, "although it should be taken to mean some percentile of a tolerance distribution with respect to some objective definition of clinical toxicity," and the "implicitly intended" percentile seems to be the 33rd percentile (related to 2/6). Storer (1989) also considered three other "up and down" sequential designs for quantile estimation in the bioassay literature and performed simulation studies of their performance in estimating the 33rd percentile. Subsequent simulation studies by O'Quigley, Pepe & Fisher (1990) showed the performance of these designs to be "dismal", for which they provided the following explanation: "Not only do (these designs) not make efficient use of accumulated data, they make use of no such data at all, beyond say the previous three, or sometimes six, responses." They proposed an alternative design, called the "continual reassessment method" (CRM), which uses parametric modeling of the dose-response relationship and a Bayesian approach to estimate parameters and to sequentially determine the dose level x such that the probability $p(x)$ of a toxic event is p_0 (e.g. 1/3). It is natural to try incorporating pharmacokinetic and other covariate information, such as age, gender, performance status (e.g. Karnofsky rating) and disease duration, into the parametric model for dose-response, and to choose a prior distribution that incorporates the current state of knowledge from the medical literature and preclinical studies. Piantadosi & Liu (1996) have demonstrated in simulation studies that incorporating an additional PK parameter (AUC) into the logistic dose-response model of CRM can improve the design of a dose escalation study.

I am currently working on other enhancements of CRM, while also considering other approaches to improved Phase I and II designs. For cancer treatments, the primary objective of a typical Phase I trial is to determine the MTD and dose limiting toxicities of the treatment so that the MTD can be used for the ensuing Phase II trial to evaluate antitumor response. Since MTD seldom has a strict quantitative definition in the protocols

of these trials, defining it formally as the dose that yields a target probability of toxicity response, and using this definition of MTD for the dose to be estimated from a Phase I trial and to be used in the ensuing Phase II trial as in Storer (1989), O'Quigley, Pepe & Fisher (1990) and Piantadosi & Liu (1996), may not best reflect the clinical considerations and constraints on the trial. A traditional dose escalation design, which does not provide adequate information for estimating some quantile of the tolerance distribution, may still be sufficiently informative for estimating something else that can be used to determine the dose of a subsequent Phase II study. In particular, I believe that a Phase I study should also generate useful PK/PD information. By combining this with the dose-limiting toxicities observed, a PK/PD modeling approach can be used to determine the dose of the Phase II study, instead of using the traditional MTD as the Phase II dose. This approach involves developing a PK/PD model from Phase I/II data and using it to evaluate via computer simulations the drug's pharmacologic actions or therapeutic/toxic responses under dosing schemes not yet studied. Thus, instead of having to perform actual clinical experiments at these dosing schemes to come up with a dose recommendation for a Phase II or III trial, one can use computer experiments to search for the dose. Although one should then conduct a pilot study at this dose to check the actual performance, this simulation approach has eliminated many clinical experiments at intermediate "trial-and-error" doses. Monte Carlo methods to carry out these computer simulations efficiently are therefore of great interest in the application of PK/PD modeling to drug development. In their position paper to the American College of Clinical Pharmacology, Derendorf et al. (2000) point out that "the area of simulation science (i.e., using drug and disease models in a simulation mode to address relevant questions) is still at a very early stage in the discipline of clinical pharmacology" and that "pharmaceutical science educational programs should actively integrate with statistical educational programs at universities."

In conclusion, drug development is moving towards increasing reliance on mathematical/statistical modeling and increasing size of data sets (measurements collected per subject, though perhaps not more subjects). Computing intensive statistical methodologies, which together with statistics in biotech research constitute the theme of the 2004 ICSA Applied Statistics Symposium, are therefore becoming increasingly important tools for tackling the complexity of new treatments and their underlying biopharmaceutical models.

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Contemporary Statistical Issues: Bioinformatics (2): Genomics (SNPs) Data

Special Topic Editor: Sue-Jane Wang, Ph.D.

*An Assessment of SNP Pharmacogenetic Component Variability in Human Drug Exposure – Individual Replicate Study Design**

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Introduction

Historically twin studies have been shown to be useful approaches to determine the heritability of persistent but variable characteristics that tend to differ among individuals.[1-3] However, an individual's response to a given drug normally disappears after elimination of the drug. The concept of variability of drug response can have a genetic cause was firmly established about 40 years ago.[4-5] With the advent of high throughput technology and recent effort of international haplotype mapping project[6] aiming at determining the patterns of closely linked single nucleotide polymorphisms (SNPs) on each individual chromosome, the complexity of genetic and genomic factors for patient-to-patient and between-population differences plays a central role in the evaluation of drug disposition, efficacy and safety.[7-8] Examples of pharmacogenetics studies are determination of an altered drug response by genetic variation of a particular protein, e.g., drug-metabolizing enzymes[9] and, more recently, advanced techniques are also showing genetic variability of drug targets, e.g., drug receptors[10] through studies of the variability of the different forms of dopamine, serotonin, or other G-protein-associated receptors.[11]

Variability in data collected from a random sample of healthy individuals in a cross-sectional study is random, although each individual has his/her own unique genetic contribution to the measurement of interest. It is possible to study the variability due to individual genetic contribution when the data are repeatedly collected over time, e.g., individual bioequivalence studies (sometimes called average bioequivalence studies) containing s-sequence, p-period, two-formulation replicate pharmacokinetic study design.

Pharmacogenetic Component Variability

Kalow et al.[12] articulated that drug effect in human is temporal. They proposed an alternative design to traditional twin studies, i.e., individual repeated drug administration (RDA) design or sometimes called individual replicate design and hypothesized that individual replicate design can substitute for twin studies in drug research. We use available individual bioequivalence pharmacokinetic study database in light of the RDA design to assess the pharmacogenetic component variability in drug disposition.[13,14] We decompose the pharmacokinetic outcome measurement variability into two types: variability attributed to between subjects that is calculated at each cross sectional time point (between-subject variability) and variability attributed to within subjects that is computed across the time points studied (within-subject variability) to evaluate the magnitude of the genetic contribution to variability in the reference drug.

We explore the contribution of the variability in pharmacokinetic measurements obtained from the individual replicate design. In the repeated drug administration model[12,15,16] in healthy individuals, the following assumptions are posed: no sequence effect and no period effect, and the effect of test product is assumed not carried over to the effect of reference product in any of the sequences studied. The primary interest is that a pharmacokinetic effect is to be explained by either the environmental and/or genetic influences.

Individual Bioequivalence Pharmacokinetic Studies

A total of 43 individual bioequivalence studies was used.[13,14] The design of these study protocols is generally standardized, a two-sequence, two-formulation, four-period, replicate study design, with a few having four-sequences. Normal healthy males and females were recruited into the study. The total number of subjects in the study was in the range of 16 to 65. After an overnight fasting, the subjects were dosed with a specific strength of the drug products with 240 ml or 8 oz. of water. The subjects were randomized to receive either the sequence alternating the test drug product and the reference drug product or the sequence alternating the reference product and the test product.[17] Serial blood samples were drawn at specific intervals at least up to 3 elimination half-lives. Meals were given 4 hours after dosing. After an adequate washout period, the next treatment according to the specific sequence was administered with water under fasting conditions and serial blood collection was carried out. This procedure was repeated at all four periods. The washout period appears to be more than adequate, i.e., at least 3 elimination half-lives so as to minimize the probability of drug effect carryover.

The analytes evaluated included parent drug for all cases and metabolites in some cases. The drug products were those reference listed drugs, known as innovator products. Three pharmacokinetic bioequivalence variables from these data sets were available for evaluation. They were area under the plasma time concentration curve from drug administration up to time t (AUC-t), AUC up to time infinity (AUC-inf), and peak concentration (CMAX). We choose AUC-inf, an index of systemic exposure, as the pharmacokinetic metric for the evaluation of drug effect. In these bioequivalence studies, study drugs included were substrates for Cytochrome P450 (CYP) enzyme system, e.g., CYP 2C9, CYP 2C19, CYP 2D6, CYP 3A4, and UGT 2B7. These study drugs are metabolized either by a single or multiple metabolic pathways. We also included drugs that are excreted by renal excretion with little hepatic metabolism.

The Variability Model in Individual Replicate Study Design

The statistical model proposed by Kalow et al.[12] is briefly summarized. Denote σ_b^2 the between-subject variability, σ_w^2 the within-subject variability, γ_{GC}^2 the estimated genetic contribution, viz., the percentage of variation that can be explained in the between-subject variance that is due to genetic factors. We have

$$\sigma_b^2 = \sigma_G^2 + \sigma_E^2 + \sigma_M^2,$$
$$\sigma_w^2 = \sigma_E^2 + \sigma_M^2,$$
$$\gamma_{GC}^2 = \left(\sigma_b^2 - \sigma_w^2\right)/\sigma_b^2,$$

where σ_G^2 is the variation caused by genetics, σ_E^2 the variation due to temporal environmental factors, and σ_M^2 the error variance. The above formulation assumes the temporal variability and the error of measurement are identically contributing to the between and the within individual variances.

Results

The log-transformed AUC-inf measure is used to compute the various components of the variability. We proposed a conservative classification rule based on the estimated genetic contribution index. Namely, a drug product is considered to have a relatively high pharmacogenetic effect and contrastingly a low environmental factor contribution if the value of γ_{GC}^2 is greater than 80%. When the value of γ_{GC}^2 is between 60% and 80%, a drug product is thought to have moderate effect attributed to both the genetic factor and the environmental factor. Any value of γ_{GC}^2 that is below 60% to negative infinity would make a drug product having a low to no pharmacogenetic effect and predominantly attributed to environmental stimulants. The proposed classification rule is applied as shown in Figure 1 wherein γ_{GC}^2 is sorted from the largest (close to 100%) to the smallest percentages (negative value). It appears that our finding based on the empirical classification rule is consistent with the literature publication in those drug products that are substrates for hepatic enzymes, indicating a moderate to strong genetic contribution to variability in drug disposition ($\gamma_{GC}^2 > 80\%$). These substrates are known to have gene variants affecting enzyme activity, e.g., CYP 2D6. Reference drug products classified in this high pharmacogenetic effect are, e.g., omeprazole, phenytoin, loratadine, morphine, propafenone, and dextroamphetamine. It is also interesting to note that those reference drug products that showed weak genetic contribution to the between subject variability ($60\% \le \gamma_{GC}^2 \le 80\%$) are those whose disposition is dependent on active transport or renal excretion.[13,14]

Extension of the Variability Model

It is worthwhile to view the model with a slight modification. That is, the environmental variance component may differ in the between- and within-subject variance. Then, the genetic contribution in the between-subject variability becomes

$$\gamma_{GC}^2 = \frac{\sigma_G^2 + \left(\sigma_{Eb}^2 - \sigma_{Ew}^2\right)}{\sigma_b^2}.$$

In this case, two temporal environmental variances are σ_{Eb}^2 (the between-subject element) and σ_{Ew}^2 (the within-subject element), respectively. When the environmental variance is the same in truth in the between- and within- variance component, the model reduces to the original RDA. The large negative value of γ_{GC}^2 is obviously caused by the much greater environmental within-variance than the sum of environmental between-variance and the genetic variance. A caveat in this formulation is the possibility of overestimation of genetic contribution. This occurs when the between-variance is much larger than the within-variance in the environmental component.

Conclusion

Effectiveness and safety of drug therapy is highly dependent on dose and resulting plasma drug concentrations. In general, an individual's response to a drug is the complex combination of both genetic and non-genetic factors including environmental and physiological factors (e.g, Lu[18]). Although environmental factors also influence the effect of medication, between-individual differences in drug response are due to sequence variants in genes encoding drug metabolizing enzymes, drug transporters, or drug targets (e.g., Xie et al.[19]). Variation in DNA sequences (i.e., SNP polymorphism) explain some of the variability in drug metabolizing enzyme activities which contribute to alterations in pharmacokinetics of drugs and impacts patients' response to drug therapy. Interestingly, the pharmacogenetic component variation explored from the available 43 individual bioequivalence pharmacokinetic studies using repeated drug administration model is consistent with known literature report on the strong versus weak genetic control of substrates evaluated. It appears that this data suggest that individual replicate design pharmacokinetic studies can be recommended in drug development to assess genetic impact on AUC or exposure-response relationships.

Further application of RDA to pharmacodynamic studies may be warranted for exploring the impact of genetic control in drug efficacy and safety. The preliminary results on the empirical magnitude of genetic contribution revealed from pharmacokinetic and pharmacodynamic clinical trials may support the clinical development decision on whether to move forward seeking candidate genes in pharmacogenomic/pharmacogenetic drug trials.

Acknowledgement

The authors wish to thank Dr. Rabi N. Patnaik for his helpful comments. This research work was supported by the RSR #03-12 funds, awarded by the Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

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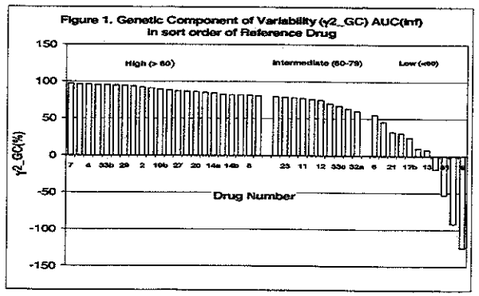

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Computing SNP Allele and Haplotype Frequencies from ESTs?

Szu-Hsien Lu, Ph.D.,
Ming-Jing Hwang, Ph.D.*

Introduction

Our phenotypic differences and disease risks are largely due to variations in the genome. The thrust of post-genomics research has therefore been to characterize human genome variations at an ever-increasing resolution and associate them with diseases. The most common form of human genetic variation is single nucleotide polymorphism (SNP); "common" SNPs are seen in greater than 1% of the population at approximately every few hundred nucleotides of the genome and show a largely similar distribution between different ethnic populations. Owing to their high density and universality, SNPs offer an unprecedented possibility for developing powerful statistical tools to map disease genes.

Information on a large number of SNPs is required for statistical significance in studies on disease, but the extremely large number of common SNPs (estimated as about 10 million) presents a tremendous economic and technical challenge for existing technologies. A number of recent studies therefore turned to characterizing the genomic distribution of SNPs and discovered that particular sets of SNP alleles are found as large co-inherited genomic blocks on a single chromosome (e.g. 1-3). These are called haplotype blocks. As it is much cheaper to work with these haplotypes in association studies, an international collaborative haplotype mapping project, HapMap, is being vigorously pursued with a scheduled completion date of 2005.[4] The project aims to genotype one million or more common SNPs and determine their allele frequencies to facilitate the statistical modeling of the combinatorial (i.e. haplotype) pattern of these SNPs. Here, we briefly review the current status of public-domain SNPs for which allele frequency data are available and comment on the potential use of expressed sequence tags (ESTs) in the bioinformatics mining of SNP allele frequency and haplotype patterns.

Current SNP allele frequency data

A number of SNP databases are available in the public domain. Together, they contain several million SNP sequences and the number continues to increase rapidly. However, only a very small fraction of these SNPs have been characterized in terms of allele frequency. For example, the latest version (release 15.0, July 23, 2003) of HGVase (Human Genome Variation Database, http://hgvbase.cgb.ki.se/) contains close to 3 million SNPs, but the allele frequency is known for less than 1.5% of these. dbSNP, the largest SNP database hosted by the National Institute of Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/SNP/), has compiled more than 9 million non-redundant RefSNPs, but less than 0.6 million (7%) come with allele frequency data. ALFRED (The ALlele FREquency Database, http://alfred.med.yale.edu/alfred) focuses on allele frequencies in diverse anthropologically defined populations, but the database is still very small (967 polymorphisms across 356 populations).

Inconsistency between different data sources is also a problem. For example, TSC (The SNP Consortium, http://snp.cshl.org/), which is included in the HapMap project, recruited six organizations to discover common SNPs in three major populations (African American, Asian, and Caucasian) and determined the allele frequency using various sample sizes ranging from 12 to 95 individuals. Based on our analysis, about 5% of the SNPs discovered for each of the three populations overlapped (i.e. were discovered independently by two or more organizations), and about 10% of these overlapped SNPs were assigned with a different major allele by the different organizations.

An EST-based approach

As most haplotype detection methods depend on SNP allele frequency, it is pertinent to develop bioinformatics approaches for the in silico prediction of SNP allele frequency. dbEST (http://www.ncbi.nlm.nih.gov/dbEST/) is an obvious choice for this purpose, as it is a very rich sequence database and has already been used for several useful bioinformatics applications, including the discovery of SNPs by examining overlapped EST sequences (e.g. 5-7). In principle, the allele frequency can also be estimated by counting the number of ESTs exhibiting a specific allele at SNP sites. Qiu et al.[8] described such an approach to compute the SNP allele frequency from ESTs and identified ~5000 SNPs for which the computed allele frequency is higher in tumors than in normal tissues, including several that have previously been shown to be associated with carcinogenesis. A comparison between the EST-estimated allele frequency and the experimental frequency, as reported in dbSNP for ~10,000 coding SNPs, showed that the in silico approach

correctly identified the major allele type for 77% of these SNPs, with disagreements between the methods being concentrated in those mapped by only a few ESTs (our unpublished data).

By mapping the genomic positions of both sequences (SNP and EST), the SNP-based haplotype of each EST clone can also be deduced. Such a bioinformatics analysis performed recently by ourselves (using dbEST #071003 and dbSNP build 115) yielded >60,000 haplotype sets, each consisting of at least two SNPs (unpublished data). Although the majority of these haplotype sets are quite small (< 1 kb) because of the size of typical EST clones, they provide a set of genome-wide, gene-centered haplotype templates that could prove useful for experimental haplotype analysis and for disease gene mapping research. Interestingly, a comparison with a set of experimentally determined haplotypes for chromosome 21[2] showed that the EST-based approach identified half of the reported haplotype patterns defined on shared SNPs (SNPs found in (8) that are also cross-referenced by EST). Furthermore, most (88%) of the EST-derived haplotypes were common haplotypes, as they were seen in 80% of the chromosomes sampled in the experimental study.

Conclusions

Despite certain pitfalls, such as having high sequencing errors and being incomplete transcripts, ESTs have been successfully used for the prediction of genes, alternative splicing, gene expression level, SNPs, and other genetic variations. In each of these bioinformatics applications, the inherent pitfalls of the EST data are handled by careful statistical analysis and modeling. The preliminary analysis described in the previous section suggests that SNP allele frequency and haplotype may also be mined from ESTs. As data on biological sequences continue to grow exponentially, the EST-based approach for predicting allele frequency and haplotype will become even more attractive and will be able to complement and aid experimental design. Statisticians will once again be called upon to develop robust bioinformatics methods for this important application.

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Some Statistical Challenges in Elucidating the Role of SNPs in Pharmacogenomics Studies of Complex Diseases and Drug Responses

Kim E. Zerba, Ph.D.

Single nucleotide polymorphisms (SNPs) are the most common type of genetic polymorphism in the human genome. The common complex diseases which are the focus of many drug therapies have etiologies that result from the combinations of interindividual variations in many genes and environments . Knowledge and analyses of SNPs in pharmacogenomics studies may facilitate the discovery of which genes are involved in complex diseases and new targets for therapy as well as the development of safer, more effective compounds. Studying interindividual variation in SNPs in relation to interindividual variation in drug response may lead to the possibility that subgroups of subjects in the population may be identified that would be more appropriate to receive the drug than others. There is a fundamental tension developing between the traditional treatment of the average of the population with the desire to treat the individual.[1] This paper is not intended as a comprehensive review and will focus on some of the key statistical problems faced by pharmacogenomics studies of complex human disease and drug response using SNPs.

Technological advances have resulted in unprecedented capabilities to measure human genetic variation. There are more than 10 million single nucleotide polymorphisms (SNPs) located in high density within and among 30,000 or more genes across the human genome that could be assessed for each individual in a study. This capability greatly exceeds that of any of the other technologies such as transcriptional profiling or proteomics. There are numerous statistical challenges that are specific to genetic studies involving SNPs, including frequency dependencies among SNP alleles because they are passed together on chromosomes from generation to generation that results in a shared evolutionary history. [2-10] The shared evolution among polymorphisms has many implications for the development of statistical methods and design of clinical trial studies.

Use of haplotypes from candidate genes, which are a collection of SNP or other polymorphism alleles that travel together from generation to generation within the gene chromosome region, have been a primary alternative approach to assessing the association of individual SNPs one-at-a-time with complex disease and drug response. Haplotypes implicitly account for these frequency dependencies among SNPs within chromosomes. Haplotypes are also potentially valuable because they are directly connected to the protein products, genetic variation in populations is inherently structured into haplotypes and they serve as a natural source of dimension reduction relative to the consideration of association tests of individual SNPs.[11] Haplotypes or their frequencies, however, must be inferred statistically in the absence of family data. This is tremendously difficult computationally when many SNPs may be involved and, if haplotype inference is not accurate, may compound errors in association inferences.

Clinical trials are composed of individuals from different race or ethnic populations that may also differ in the frequencies of relevant genetic polymorphisms, which presents additional statistical challenges. The traditional self-reported race or ethnicity labels may not be an accurate reflection of the underlying genetic structure and statistical approaches to account for such genetic stratification in the analyses may be necessary to help avoid spurious associations.[12-15]

There is a controversial issue regarding the use of candidate genes. The problem is that the genes are usually chosen because of some *a priori* knowledge about the possible role of the gene in the biology being studied. Such an identification is usually not exhaustive in terms of consideration of the potential numbers of genes that may be involved. For every candidate gene, one only has to consider the possible genes that are within a few degrees of biological network connection to the candidate gene in question to realize that there may be hundreds to thousands of other candidate genes that might also be involved. This realization has led to increased attention to using a collection of SNPs which could cover the entire genome in an efficient way such that these other possibilities are captured. Focus on efficiency here has meant that one approach to such a collection would take advantage of the frequency dependencies among SNPs where redundancies among SNPs that are highly correlated with each other in haplotype blocks are eliminated from consideration.[16] Such a collection of SNPs may still represent 100,000 to more than a million SNPs and presents tremendous problems in cost of genotyping individuals as well as use of precious DNA from subjects, which can be limiting.

DNA pooling is one approach that may be cost effective for a panel of SNPs from the entire genome as a screening tool in reducing the number of SNPs that need to be genotyped on each

subject.[17] Such an approach relies on a binary trait, such as disease presence or absence. The DNA from subjects with the disease is combined in one pool and those without the disease in the other pool. SNP allele frequencies from the entire panel of SNPs are then assessed in multiplex from each pool and associations with disease tested by comparing allele frequencies for each SNP. This is analogous to genotyping only two individuals for the panel of SNPs. An additional small balanced number of technical replicate pools may be used to increase confidence in the frequency estimations. Significant associations observed for a smaller number of SNPs in the panel may then be identified for follow-up individual genotyping. As the cost of DNA pooling approaches comes down, it will likely result in the end of domination by candidate gene studies as the first step in assessing the role of genetic variation in disease susceptibility and drug response.

All of the approaches described above are plagued by multiplicity problems. These problems are not unique to genetic studies using SNPs. There have been significant developments,[17-21] however, false positive and negative results are likely to be a common feature[23] of such massive studies compared to the relatively small sample sizes that will be typical of most studies for the foreseeable future. There has been a call for more emphasis on multiple studies of SNP associations and the use of meta analysis to assess evidence for replication.[24] Such an approach will require a more long term probability view to replication of SNP association results than is currently recognized.

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Regional Activities

Hong-Kong

Hailiang Yang, Ph.D.

Conference on Insurance Mathematics, Ruin Theory and Monte Carlo Methods, 28-30 June 2004:

This conference was jointly organized by the Department of Statistics and Actuarial Science and the Institute of Mathematical Research, Department of Mathematics, HKU, the captioned conference was held from 28-30 June at the University of Hong Kong. The Conference featured many leading experts and distinguished speakers, among whom are Hans Gerber, Marc Goovaerts, Tse-Leung Lai and Elias Shiu, etc. The Organizing Committee includes: T.L. Lai (Stanford and HKU), K.W. Ng (HKU), N.H.Chan (CUHK), Elias Shiu (U of Iowa and HKPU), H.Yang (HKU) and S.P. Yung (HKU). For more details, please go to the conference's website. The website address is http://hkustasc.hku.hk/users/irm/

Threshold models and new developments in time series

A conference entitled "Threshold models and new developments in time series', was held at the University of Hong Kong on July 12-14, 2004, in honour of Professor Howell Tong. The Organizing Committee includes: K. W. Ng, H.Z. An, K.S. Chan, N.H. Chan, T.L. Lai, W.K. Li, R.S. Tsay, Q.W. Yao. Speakers include many leading experts in time series and related areas. For details please go to the conference website at: http://hkustasc.hku.hk/users/ndts/

The Third International Congress of Chinese Mathematicians (ICCM 2004)

The Third International Congress of Chinese Mathematicians was held in Hong Kong from December 17 to December 22, 2004. The Congress was sponsored by The Morningside Group. It was organized and sponsored by The Institute of Mathematical Science and the Department of Mathematics at The Chinese University of Hong Kong. It was supported by the sister universitites in Hong Kong and also the Mathematics centers at Academica Sinica and Zhejiang University. The Congress Chairman was Professor Shing-Tung Yau. Professors Jianqing Fan and Tze Leung Lai were plenary speakers at ICCM, and ten other statisticians and probabilists gave 45-minute invited talks. For more details, please visit the conference website at: http://www.ims.cuhk.edu.hk/conference/iccm 2004/

Workshop on Probability with Applications to Finance and Insurance (II), December 15 2004:

This is the second workshop on probability with applications to finance and insurance. The workshop was held on December 15, 2004 at the University of Hong Kong. There were 8 invited talks in both theoretical and applied probability during the workshop. Professor Tze-Leung Lai, H. Yang and S.P. Yung were the organizers of the workshop. Prof. Lai is visiting the Department of Mathematics, University of Hong Kong as C.V. Starr Professor from December 10, 2004 to January 15, 2005. The workshop website address is: http://www.hku.hk/math/imr/

International Workshop in Financial Mathematics and Statistics, December 16, 2004

The Hong Kong Polytechnic University organized an international workshop in financial mathematics and statistics. The workshop was held on December 16, 2004. Prof. Teo, head of department of applied mathematics, was the chairman of organizing committee. Professor Elias Shiu gave an opening talk and 6 invited speakers presented papers on financial mathematics or statistics. For more details, please visit the workshop website at: http://www.polyu.edu.hk/%7Eama/even_frm.htm

Workshop on Statistics and Probability 2005, January 4, 2005:

The Hong Kong University of Science and Technology is organizing a workshop on statistics and probability. Prof. Alberta Lo is the organizing committee chair. Speakers include Professors T. L. Lai, R. Miura and others from USA, Japan, Korea, Singapore, Taiwan, Mainland China and Hong Kong. The workshop will be held on January 4, 2005 at the HKUST. The website address if the workshop is: http://www.bm.ust.hk/~stat2005

Professor Zhiliang Ying won the Morningside Gold Medal at ICCM

At the opening ceremony of the Third International Congress of Chinese Mathematicians will be held in Hong Kong on December 17, 2004, it was announced that Professor Zhiliang Ying, Columbia university, was the co-winner of the 2004 Morningside Gold Medal of Applied Mathematics at the ICCM; the other co-winner was Thomas Hou, a numerical analyst and applied mathematician at Caltech.

Hailiang Yang, Ph.D. is Associate Professor of the Statistics and Actuarial Science Department, The University of Hong Kong.
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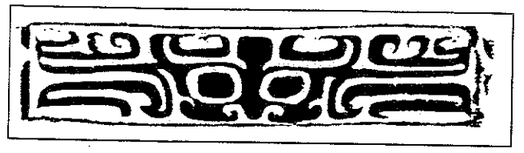

Taiwan

C. Andy Tsao, Ph.D.

Workshop in honor of Dr. T.Y. Hwang's Retirement
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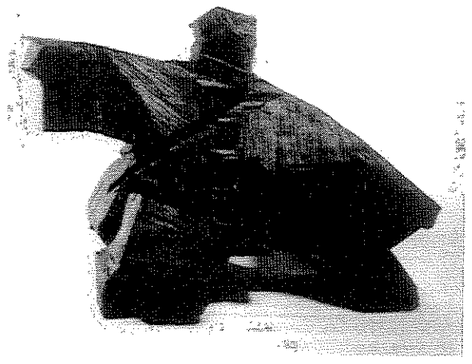

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The deadline is February 28, 2005 (see ICSA website at http://icsa.org/icsa2005/ for detailed information). For further questions, please contact Prof. Grace Yang, University of Maryland, email: gly@math.umd.edu

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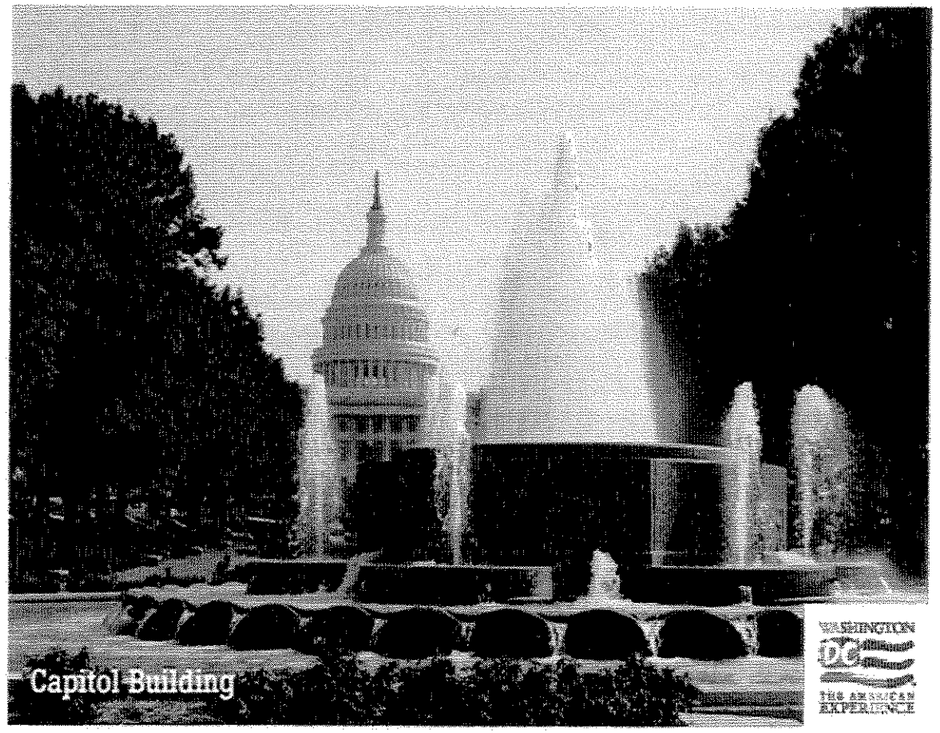
Jinbo Chen, Ling Chen, Gang Cheng, Milton Fan, Shibo Feng, Ping Hu,
Hsien-Ming James Hung, Jia-Wen Ko, Chenxiong Le, Hung-Ir Li, Shiu-Hua Li, Zhao Hai Li,
Stan Lin, Aiyi Liu, Ming Tang, Sue-Jane Wang, Colin O. Wu, Lap-Ming Wun, Grace Yang,
Treasurer and Registrar: Milton Fan, fanm@cder.fda.gov, (301) 827-3088
Program Committee: Hsien-Ming James Hung (Chair), hung@cder.fda.gov, (301) 594-5436
Contributed papers: Aiyi Liu, liua@mail.nih.gov, (301) 435-6953
Student Award Committee: Grace Yang (Chair), gly@math.umd.edu, (301) 405-5480
Short Course Committee: Ling Chen (Chair), chenli@cder.fda.gov, (301) 827-3486
Logistic Committee: Shiu-Hua Li (Co-Chair), sli@nida.nih.gov, 301- 443-9811,
Lap-Ming Wun (Co-Chair), lwun@ahrq.gov, 301-427-1670
Proceedings: Sue-Jane Wang (Chair), wangs@cder.fda.gov, (301) 827-3089
J.P.Hsu Memorial Scholarship: Sue-Jane Wang, wangs@cder.fda.gov, (301) 827-3089
On-site Registration Committee: Zhao Hai Li (Chair), zli@research.circ.gwu.edu



Washington, D.C.

ICSA 2005 APPLIED STATISTICS SYMPOSIUM PRELIMINARY PROGRAM

Session Titles & Speakers	Organizer & Chair
Methods and Practice of Genomic Statistics Frank Shen, Wei Pan, Sue Li	Lu-Ping Zhao
Variance Component	Naitee Ting
Statistical Approaches for Gene (or proteomic) Expression Signature Biomarker Validation Yu Shyr, Sue-Jane Wang	Sue-Jane Wang
Biased Sampling Models and Their Applications Song Xi Chen, Fanhui Kong, Jing Qin	Jian-Lun Xu
Screening for Cancer	Ping Hu
Small Area Estimation: Theory and Applications Jai Won Choi, P. Lahiri, Lou Rizzo, Dawei Xie	William Chen
Missing Data & Longitudinal Data	S. Edward Nevius
Bayesian Modeling and Monte Carlo Methods David B. Dunson, Faming Liang, Min-Hui Chen	Ming-Hui Chen
Clinical Trial Design Sue-Jane Wang, Guoxing (Greq) Soon	Charles Le
Advances in Survival Analysis Gang Li/Qihua Wang, Jianguo Sun, Jiantian Wang	Hongbin Fang
Industrial Statistics Gang Zheng, Peihua Qiu, Andrew Rukhin, Refik Soyer	Gang Zheng
Pooling Biospecemens: Methodologies, Applications and Limitations Joanna H. Shih, Peter Song, Enrique F. Schisterman	Aiyi Liu
Pharmaceutical/Device Safety Studies Ling Chen, Joanne Zhang, James Chen	Ling Chen
Recent Developments in Statistical Methods for Medical Diagnosis Yingye Zheng, Aiyi Liu, Andrew Zhou	Tianxi Cai
JP Hsu's Student Paper	Sue-Jane Wang
Enhancing Preclinical and Clinical Research Interaction to Accelerate Drug Development	Ming Tan
Biostatistical Advances in Taiwan	Chao Agnes Hsiung
Biostatistical Advances in China	
Career Planning – Writing Grant Proposal	Grace Yang
Career Planning – Industry Employment	

Career Planning – New Ph.D Statistician	
Statistical Applications in Biological Product Research	Tony Lachenbruch
Statistical Applications in Medical Device Research	Greg Campbell
Statistics for Nanotechnology Kevin J. Coakley, Don Malec, Z.Q. John Lu	John Lu
Statistical Genetics Nilanjan Chatterjee, Xin Tian, Christoph Lange, Nancy Glenn	Gang Zheng
Nonparametric Methods for the Analysis of Longitudinal Data John Rice, Jane-Ling Wang, Jianhua Huang, Jeffrey Morris	Colin Wu
Quality Control I – Quality by Design	Jeff Wu
Pharmaceutiocal Quality Assessment Roswitha Kelly/Ted Kuo, Meiyu Shen, Yi Tsong	Yi Tsong
Non-Clinical Statistical Applications in the Pharmaceutical Industry Nandini Raghavan, D. Raghavarao, Jyh-Ming Shoung	Stan Altan
Success of Phase III Clinical Trials	Robert O'Neill
Project Management of Drug Development	Charles Anello
Cancer Clinical Trials Kao-Tai Tsai, Lu Ying, Yong Lin	Weichung Joe Shi
Statistical Issues in Proteomics Analysis Used in Biomarker Research	Frank Shen Li-An Xu
Benefit-Risk Evaluation of Clinical Development Projects: A Financial Perspective Yilian Yuan, Xiaolong Luo, Qing Liu	Qing Liu
Active Control Trial H.M. James Hung, George Y.H. Chi, Joshua Chen	Ivan Chan
Data Monitoring Committee: Issues and Practice Weiying Yuan, Jerry Gardner, Gordon Lan, Robert O'Neill (Discussant)	Irving Hwang
Recent Advances of Nonparametric Regression Techniques, With Applications in Biological and Geological Sciences Chun Han, Hua Liang, Jing Wang	Lijian Yang/ Hua Liang

ICSA 2005 APPLIED STATISTICS SYMPOSIUM
Short Courses

Course 1: *Statistical Inference for Quality-Adjusted Lifetime*

Instructor: ***Hongwei Zhao, Sc.D.***
Department of Biostatistics and Computational Biology, University of Rochester

Course Outline:
In the treatment evaluations of chronic diseases, such as cancer, AIDS, or cardiovascular diseases, extending overall survival time may not be the only goal of a new therapy. For example, cancer patients might have to endure a long time of toxicity from a drug; and life after disease recurrence might be painful. Similarly, a new cardiovascular device might prolong a patient's overall survival time, but it can also cause more hospitalizations for the patient. The concept of quality-adjusted lifetime (QAL) has received much attention recently. In this short course, I will discuss the motivation for using the measure QAL, and the difficulties encountered in making inference about QAL with censored data. I will present methods for estimating the survival distribution of QAL, and methods for testing the difference of QAL from two or more samples, when independent right-censoring is present. I will also discuss regression problems with QAL. Simulation studies and examples will be presented to illustrate the methods.

About the Instructor:
Hongwei Zhao, Sc.D. completed her Sc.D in Biostatistics at Harvard School of Public Health in 1997. She is an Associate Professor of the Department of Biostatistics and Computational Biology at University of Rochester. Her research interest is on statistical methods for survival analysis, and longitudinal data analysis. She has published many articles on the topic of quality adjusted lifetime analysis.

Course 2: *Design and Analysis of Microarry Experiments*

Instructor: ***Mei-Ling Ting Lee, Ph.D.***
Department of Biostatistics
Harvard University

Course Outline:
1. Introduction: Genome Probing Using Microarrays
 a. DNA, RNA, Proteins, and Gene Expression
 b. Microarray Technologies
 c. Inherent Variability in Microarray Data
 d. Background Noise and Normalization
2. Statistical Models and Case Studies
 a. Experimental Design for Microarray Studies
 b. Two-stage ANOVA Models for Microarray Data
 c. Bayesian Methods for Microarray Data
 d. Multiple Testing in Microarray Studies
 b. Permutation Tests in Microarray Data
 e. Power and Sample Size Considerations
3. Supervised and Unsupervised Exploratory Analysis:
 a. neural network
 b. self-organizing Maps
 c. support vector machines

Textbook:
Lee, Mei-Ling T. (2004) *Analysis of Microarray Gene Expression Data,* published by Kluwer Acacemia Publishers (under new management by Springer-verlag).

About the Instructor:
Dr. Lee is an Associate Professor in Medicine (Biostatistics), Harvard Medical School; an Associate Professor in the Department of Biostatistics, Harvard School of Public Health; and a Biostatistician at Brigham and Women's Hospital, Boston, Massachusetts, USA. Dr. Lee completed her Ph.D. degree at University of Pittsburgh, 1980. Recently, Dr. Lee has written a book titled *Analysis of Microarray Gene Expression Data* (2004) published by Kluwer Academic Publishers. Dr. Lee is the Founding Editor and Editor-in-Chief, *Lifetime Data Analysis* (1994-present). She is a member of the International Statistical Institute (1995); Fellow of the Royal Statistical Society, U.K. (1998); Fellow of The American Statistical Association (1999), USA; and the *Mosteller Statistician of the Year* 2005, American Statistical Association, Boston Chapter.

Course 3: *Interim analyses and adaptive designs in clinical trials*

Instructor: ***Gordon Lan, Ph.D.***
Sanofi-Aventis Pharmaceuticals

Course Outline:
This is an overview of sequential methods used in clinical trial design and data monitoring. We start with conditional power evaluation and stochastic curtailing, and then briefly introduce the group sequential methods and the spending functions. We consider two types of response variables: (i) immediate response variable, and (ii) time-to-event variable. Many two-sample tests for these responses, when computed over time, approximate the Brownian motion process.

For a quick review of survival data analysis, we use heuristic arguments to demonstrate that the logrank statistic evaluated over time is a martingale, or, a fair gambling process. With slight modifications, the same idea extends from the logrank to other linear rank statistics. A brief overview of adaptive (flexible) designs will be presented.

Key words: Brownian motion, stochastic curtailing, group sequential methods, spending functions, survival data analysis, martingales.

About the Instructor:
Dr. Gordon Lan received his Ph.D. in Mathematical Statistics from Columbia University. He is currently Statistics Fellow at Aventis Pharmaceuticals. Prior to joining Aventis, Dr. Lan was Distinguished Scientist at Pfizer (1995-2002), Professor of Statistics at George Washington University (1989-1995) and Mathematical Statistician at the National Heart, Lung, and Blood Institute - National Institutes of Health (1980 – 1989). He has published several articles on clinical trial design and interim data analysis. He was elected Fellow of the American Statistical Association in 1992.

Course 4: *Pharmacoepidemiology, An Overview*

Instructor: ***Yi Tsong[1], Ph.D., David J. Graham[2], M.D., Zili Li[3], M.D.***
[1]Quantitative Methods and Research Staff, Office of Biostatistics, [2]Office of Drug Safety, [3]Division of Medical Imagine and Radiapharmacy Drug Products, Office of Drug Evaluation 3, Center for Drug Evaluation and Research, Food and Drug Administration

Course Outline:
Due to the relatively small sample size of clinical trials of a new test treatment, Postmarketing safety assessment plays an important role in risk management of a drug product. It often consists of safety signaling with the ADR reporting system, epidemiologic observational study and meta safety analysis of clinical trials. The course consists four 90-minutes segments.

Segment 1 –
A. Signaling procedures with the adverse reporting system:
- Signaling with ratio of reporting rates

- Qualitative and quantitative data mining.

B. Classical case-control and cohort studies:
- Choice of the design
- Sample size determination and concerns
- Basic analysis methods

C. Safety meta analysis of clinical trials:
- Background incidence rate
- Patient inclusion criteria
- Effect of enhanced population
- Placebo control and active control
- Regional difference
- Multiple treatments
- Multiplication and additive model

Segment 2 – Case studies of (drug name)
Case-control and cohort studies. An overview of study design methods for case-control and cohort studies will be presented followed by two illustrations: cohort study-rhabdomyolysis risk with lipid-lowering drugs; case-control study-myocardial infarction risk with COX-2 drugs and traditional NSAIDs.

Segment 3 – Interactive workshop on key principles of the drug risk assessment – can you resist the temptation of data pooling or should you? Data pooling or meta-analysis is a commonly employed analytical strategy in drug risk assessment, especially for assessing those infrequent adverse drug events. Through a case study of a drug-induced ischemic colitis, this workshop is designed to illustrate the importance of understanding the clinical and epidemiological principles of the drug risk assessment.

Segment 4 –
A. A case study of PPA and stroke:
- OTC drugs and grand father law
- Signals from reporting system
- Design issues of a case-control study
- Analysis of data
- Advisory Committee discussion and decision

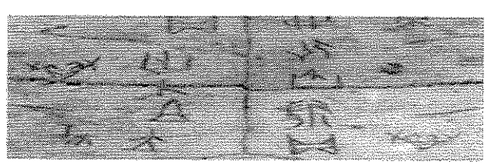
B. Non-inferiority testing approach:
- Hypotheses
- Sample size consideration
- Analysis
- Interpretation

About the Instructors:

Yi Tsong, Ph.D., is currently a mathematical statistician of Quantitative Methods and Research Staff of CDER, FDA. He specializes in postmarketing risk assessment and quality assurance. He received CDER and FDA level awards for contributions in postmarketing drug risk assessment, for advisory on CDER postmarketing risk assessment external contracts, medication errors, quality control evaluation, drug compliance, in vitro bioequivalence, adaptive design and non-inferiority tests. Dr. Tsong is currently the President Elected (2006) of ICSA. He received his Ph.D. in Mathematical Statistics from The Univ. of North Carolina-Chapel Hill in 1979.

David J. Graham, M.D., M.P.H, is a physician-epidemiologist at FDA, with 20 years experience in pharmacoepidemiology. He is currently the associate director for science in the Office of Drug Safety.

Zili Li, MD, MPH is a board-certified physician in preventive medicine with a special interest and expertise in IND and NDA review, including both efficacy and safety assessment. He currently serves as a medical team leader with the office of new drugs at the FDA and is a member of FDA's pre-marketing drug risk assessment working group. Dr. Li was a recipient of many FDA awards, including 2003 FDA Scientific Achievement Award because of his innovative approach to safety-related meta-analysis of clinical trial data. In addition to his medical degree, Dr. Li has also received two Master's degrees in public health, including one from the Johns Hopkins School of Public Health. Prior to joining FDA, Dr. Li had worked as an epidemiologist for more than seven years and co-authored many peer-reviewed articles.



Course 5: *Statistical Analysis of Incomplete Longitudinal Data*

Instructor: ***Daniel F. Heitjan, Ph.D.***
Department of Biostatistics & Epidemiology,
University of Pennsylvania

Course Outline:

Incompleteness of one kind or another is a common feature of data sets gathered in many areas of research. The development of methods for analyzing incomplete data has been an important focus of biostatistical research over the last several decades. This short course will review the theory and methodology of incomplete data, with a particular emphasis on longitudinal data. We will cover the following topics: ignorability, including MAR and MCAR; simple methods for handling incomplete data under ignorability, such as the linear mixed model; methods based on imputation; pattern-mixture models, particularly in the context of studies where some subjects may die before completing the planned observations; nonignorable modeling; and the new field of diagnostics for sensitivity to nonignorability. We will touch on related ideas from Bayesian analysis, statistical computing and causal modeling. The course will emphasize practical approaches and real-world applications.

The suggested text is Little RJA, Rubin DB (2002). *Statistical Analysis with Missing Data*, 2nd edition. New York: Wiley.

About the Instructor:

Daniel Heitjan completed his Ph.D. in Statistics at Chicago in 1985. He is currently Professor of Biostatistics and Statistics at the University of Pennsylvania, and Director of the Biostatistics Resource in the Abramson Cancer Center. He previously served on the faculties of Columbia University, Penn State, and UCLA. Dr. Heitjan's research interests include the theory and methodology of incomplete data, longitudinal modeling, clinical trial design and analysis, Bayesian analysis, and most recently the statistical methodology of health outcomes research and health economics. He is a member of the editorial boards of *Statistics in Medicine* and *Journal of the National Cancer Institute*, and serves on the AHRQ Health Care Technology & Decision Science study section. A fellow of the American Statistical Association, he is Program Chair for the 2005 Joint Statistical Meetings. Dr. Heitjan serves on numerous clinical trial data monitoring committees and consults regularly with the pharmaceutical industry.

Course 6: *Generalized Linear Latent and Mixed Models*

Instructors:
Sophia Rabe-Hesketh, Ph.D., UC Berkeley
Anders Skrondal, Ph.D., Norwegian Institute of Public Health

Course Outline

Generalized linear mixed (or multilevel) models (GLMMs) are useful for longitudinal data, cluster-randomized trials, surveys with cluster-sampling, genetic studies, meta-analysis and many other applications. The random coefficients in GLMMs are latent variables representing between-cluster variability and inducing within-cluster correlations.

Latent variables are also often used to represent true values of variables measured with error, e.g. diet (continuous) or diagnosis (categorical). Measurement models specifying the relationship between measured and latent variables (factor, item response or latent class models) can form part of regression models, giving structural equation models (SEMs), such as covariate measurement error models. SEMs can also be

used to model dependence between different processes, for instance the response of a clinical trial and drop-out. Taking a unified view of all these models is beneficial because developments and software for one model-type are often applicable to other model-types.

This one-day course will be structured in three parts: (1) generalized linear mixed models, (2) measurement models and (3) structural equation models. The course will be based on the book *"Generalized Latent Variable Modeling: Multilevel, Longitudinal and Structural Equation Models"* by Skrondal and Rabe-Hesketh, published by Chapman & Hall/CRC, 2004.

About the Instructors

Sophia Rabe-Hesketh, Ph.D., is Professor in Educational Statistics at the Graduate School of Education, University of California, Berkeley. She is also a member of the Interdepartmental Group in Biostatistics at Berkeley and was previously a Reader in Statistics at the Department of Biostatistics and Computing, King's College London.

Anders Skrondal, Ph.D., is Head of the Statistics Group at the Division of Epidemiology, Norwegian Institute of Public Health, Oslo. He was awarded the "1997 Psychometric Society Dissertation Prize" for his Doctor Philos. in Statistics.

Sophia Rabe-Hesketh and Anders Skrondal have been collaborating for the past five years. They have developed a general modeling framework (GLLAMM) for hierarchical and latent variable modeling described in their book on "Generalized Latent Variable Modeling: Multilevel, Longitudinal and Structural Equation Models" (Chapman & Hall/CRC, 2004) and in numerous papers published in journals including Psychometrika, Biometrics, Journal of Econometrics, and Statistical Modeling. The models in the framework can be estimated using a Stata program **gllamm.**

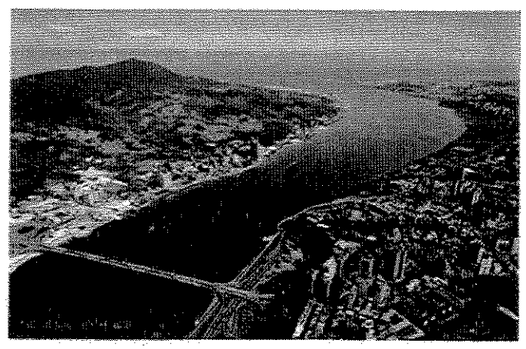
Career Opportunity

TAMKANG UNIVERSITY
Department of Mathematics
Faculty Position

The Department of Mathematics at Tamkang University invites applications for a position starting August 1, 2005. Applicants must have a Ph.D. in Mathematics or Statistics. Evidence of scholarly potential and strong commitment in teaching and research are essential. Salary and rank will commensurate with experience and record.

Qualified applicants should send a resume (including list of publications, statement of research and teaching interests), copies of transcript (for fresh Ph.D's) and three letters of reference by February 15, 2005 to:
Chairman, Department of Mathematics,
Tamkang University, Tamsui, Taiwan 251
Tel: (886)-2-26215656 ext. 2502;
Fax:(886)-2-26209916
E-mail: chuanjen@mail.tku.edu.tw

NOTE: Chinese is the sole language used in teaching and administration at the university.



International Chinese Statistical Association
泛華統計協會

INTERNATIONAL CHINESE STATISTICAL ASSOCIATION
YEAR 2005 APPLIED STATISTICAL SYMPOSIUM

June 12-15, 2005

Bethesda North Marriott Hotel & Conference Center
5701 Marinelli Road, North Bethesda, MD 20852

Registration Form

Name: (English) _____ (Chinese, if any) _____
Affiliation: _____ Affiliation category: □ Industry □ Gov. □ Academic
Mailing Address: _____
_____
Telephone: (____)_____ Fax: (____)_____E-Mail:_____
Speaker: □Yes □ No □ Overhead □ Slide □ PowerPoint □ Other: _____

1. Symposium Registration

Please check the appropriate box below.

Membership Type	By April 30, 2005	Check (√)	After April 30, 2005	Check (√)
Member	$160	□	$180	□
Nonmember	$200	□	$220	□
Student Member	$70	□	$90	□
Student Nonmember	$90	□	$110	□

2. ICSA 2005 Membership

Nonmember attendees will receive one-year membership
For new or renewal membership: Please print Membership Application Form from http://www.icsa.org and mail it with this Registration Form.

For ICSA member attendees, please renew your membership:
Check the appropriate box below.

Annual ICSA regular membership	$ 40	□
Lifetime ICSA permanent membership	$ 400	□
Annual ICSA student membership	$ 20	□

3. Short Course Registration* (Sunday, June 12 from 9:00 AM to 5:00 PM)

*The symposium registration fee is also required for taking short course only. The fee includes breakfast and coffee breaks for AM courses (only coffee breaks for PM courses). Breakfast and lunch are also provided for the whole day courses.

Please select the short course you would like to attend:

Topics and Instructors	Non-student		Student	
	By April 30, 2005	After April 30, 2005	By April 30, 2005	After April 30, 2005
1. **Statistical Inference of Quality Adjusted Life (QAL)** (AM Session) Prof. Hongwei Zhao, *University of Rochester*	$150 □	$175 □	$25 □	$30 □
2. **Design and Analysis of Microarry Experiments** (PM Session) Prof. Mei-Ling Ting, *Harvard University*	$150 □	$175 □	$25 □	$30 □
3. **Interim analyses and adaptive designs in clinical trials** Gordon Lan, Ph.D. *Sanofi-Aventis Pharmaceuticals*	$300 □	$350 □	$50 □	$60 □
4. **Pharmacogivilance and Epidemiology: Basic Theory and Case Studies** David Graham, Ph.D., Zili Li, Ph.D. and Yi Tsong, Ph.D. *CDER, FDA*	$300 □	$350 □	$50 □	$60 □
5. **Statistical Analysis of Incomplete Longitudinal Data** Prof. Daniel F. Heitjan, *University of Pennsylvania*	$300 □	$350 □	$50 □	$60 □
6. **Generalized Linear Latent and Mixed Models** Prof. Sophia Rabe-Hesketh, *UC Berkeley* and Prof. Anders Skrondal, *Norwegian Institute of Public Health*	$300 □	$350 □	$50 □	$60 □

4. Total Conference Payment

Symposium Registration =$_____
ICSA Membership =$_____
Short Course: =$_____
Banquet on Monday night, June 13 2005:
$30/person x _____people =$_____
$15/child x _____children (under 10 years old) =$_____
Total for Banquet =$_____
Donation to ICSA =$_____

Total Payment: =$_____

Please send completed registration form with check (*payable to 2005 ICSA Applied Statistics Symposium*) **to:**

Milton C. Fan
Treasurer, 2005 ICSA Applied Statistics Symposium
10 Thorburn Place, Gaithersburg, MD 20878
Phone (301) 827-3088, E-Mail: fanm@cder.fda.gov

Cancellation Policy: Full refund for cancellation will be made if requested on or before April 30, 2005; 80% refund will be made if requested after April 30, 2005 but on or before May 15, 2005.

ICSA 2005 APPLIED STATISTICS SYMPOSIUM
Student Awards & Travel Grants

The 2005 Annual ICSA Applied Statistics Symposium will be held during June 12-15, 2005 at the Bethesda North Marriott and Conference Center, Maryland. The Program Committee will again sponsor the Student Awards and Travel Grants. The main purpose of the award is to encourage student members of ICSA to participate and present their research work at this annual meeting.

Qualifications: The student must be an ICSA member (or join at the time of manuscript submission), a degree candidate in any term during the academic year 2004-2005 at an accredited institute and be able to register and present the work at the 2005 symposium.

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

Review and Selection Process: Three review members of the Award Committee, appointed by the Chair of the Committee, will receive blinded copies of the submitted manuscripts from the Committee Chair and review them based on the following criteria:

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

Up to 3 travel award winners will be selected by the Awards Committee chaired by Professor Grace Yang. Each winner will receive a certificate, $400, and tuition for one short course of his/her choice. Winners will be notified by April 20, 2005.

Submission of Manuscripts: Manuscripts should be received and postmarked no later than February 28, 2005. The submission should include:

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

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

Professor Grace Yang, (gly@math.umd.edu)
Department of Mathematics
University of Maryland
College Park, MD 20742.

International Chinese Statistical Association

泛華統計協會

Membership Application & Renewal Form

Name	(Last)	(Middle)	(First)
(English)			
(Chinese)			
Address			
Office	Address:		
	City:		
	State:	Zip Code:	Country:
	Email:	Telephone:	FAX:
Home	Address:		
	City:		
	State:	Zip Code:	Country:
	Email:	Telephone:	FAX:
Education			
	Degree:	Year Graduated:	
	University:		
Professional Occupation & Title			
	Occupation:	Title:	

Membership Fees

Regular	(US$40)
Student	(US$20)
Permanent	(US$400)
Spouse	(50%)
Donations	
Total Amount Paid:	US$

Statistical Area of Interest (circle all applicable):

A: Agriculture	B: Business / Economics
C: Computing / Graphics	D: Education
E: Engineering	F: Health Sciences
G: Probability	H: Social Sciences
I: Biostatistics	N: Theory & Methodology

Please Make Check Payable to: I.C.S.A. Mail This Form & Fees to:
ICSA c/o Ivan S. F. Chan, 105 Oval Lane, North Wales, PA 19454

International Chinese Statistical Association

Profit and Loss

January 1, 2004 through December 31, 2004

Ordinary Income/Expense	
Income	
Advertisement	600.00
Donations	1,070.00
Membership Dues	5240.00
Symposium Short Course	10887.00
Miscellaneous	52.59
Total Income	**17849.59**
Expense	
Miscellaneous	
Refund to symposium account	529.5
Member services	324.93
Working lunches	110.60
ICSA web page service	1754.29
Poster designs	50.00
Plagues and plates	1715.40
Interview expense for July Bulletin	27.55
Casual labor	40.00
Total Miscellaneous	4552.27
Postage and Delivery	
Account documents	45.27
Book/journal donations	364.00
Statistical Sinica label shipping	87.65
January Bulletin	1475.71
July Bulletin	1335.51
Total Postage and Delivery	3308.14
Printing and Reproduction	
January 2004 Bulletin	3760.00
July Bulletin	3820.00
January 2005 Bulletin	1500.00
Total Printing and Reproduction	9080.00
Professional Tax Services	570.46
Total Expense	17510.87
Net Ordinary Income	338.72
Other Income/Expense	0
Net Other Income	0
Net Income	338.72

International Chinese Statistical Association

Balance Sheet

January 1, 2004 through December 31, 2004

ASSETS	
Checking/Savings	
Checking	34,625.13
Savings-Money Market	30,000.00
TOTAL ASSETS	**64,625.13**
LIABILITIES & EQUITY	
Equity	
Opening Balance Jan 1, 2004	64,286.41
Net Income	338.72
Total Equity	64,625.13
TOTAL LIABILITIES & EQUITY	**64,625.13**

A Thank You Note From the Past President, Frank Shen, Ph.D.

It has been a lot of fun to serve ICSA as its 2004 President. The pleasure came from working side-by-side with many members who I have known for years in dedication to serve the ICSA, and from those who I met the first time. I also enjoyed meeting many new members and listening to their good ideas.

I would like to use this opportunity to express my gratitude for your help and support. Please join me and continue to give support to the new President, Professor Jiahua Chen, who has worked with me closely in 2004. I would also like to thank the Directors of the Board, Chairs and members of the committees, the Executive Director, and the treasurer, for their service and dedication to the Association. I will certainly miss those heated debates from e-mails and in the Board room. Special thanks to our friend, Dr. "Fritz" Scheuren, the coming ASA President, for his effort and courage in bringing ICSA and ASA closer. As the four words I used to symbolize ICSA in the recent issue of AmStat News, 四海一家, "all people surrounded by the four seas belong to a big family," ICSA family will continue to grow and prosper.

Have a happy and productive new year!

Frank Shen, Ph.D., is Executive Director of Exploratory Development, Global Biostatistics and Programming, Bristol-Myers Squibb Company. Email: frank.shen@bms.com

Calendar of Meetings

January 12 - 14, 2005 The Second Joint IMS/ISBA International Conference
Location: Bormio, Italy (Italian Alps)
http://www.eco.uninsubria.it/IMS-ISBA-05/

June 20 – 24, 2005 International Conference on Statistics in Honour of Professor Kai-Tai Fang's 65th Birthday
Location: Hong Kong
http://www.math.hkbu.edu.hk/Fang65

Professor Kai-Tai Fang, Fellow of the American Statistical Association and the Institute of Mathematical Statistics, is the co-inventor of the uniform experimental design, which is used by engineers to expedite product development. He has discovered new methods for inference in multivariate data. In recent years he has collaborated with biologists and chemists to enhance our understanding of Chinese medicine. He is the author or co-author of six research monographs, twelve textbooks and over 250 articles that cover computational statistics, distribution theory, experimental design, growth curve models, Monte Carlo and Quasi-Monte Carlo methods, multivariate analysis, optimization, popularity, statistical graphs, statistical inference and others. As Professor Fang celebrates his 65th birthday, we are organising a conference to recognise his achievements. The conference will cover all main areas in Statistics.

July 9 - 11, 2005 The Joint Meeting of the Chinese Society of Probability and Statistics CSPS) and the Institute of Mathematical Statistics (IMS)
Location: Beijing, China
http://math.bnu.edu.cn/statprob/CSPS-IMS2005/index.html/

August 2 - 6, 2005 Eight IMS North American New Researchers Conference
Location: University of Minnesota
http://pages.pomona.edu/~jsh04747/NRC/NRC.htm

General Information: These conferences were/are organized by the IMS to promote interaction among new researchers primarily by introducing them to each other's research in an informal setting. As part of the conference, participants will present talks and posters on their research and discuss interests and professional experiences over meals and social activities organized through the meeting as well as by the participants themselves. The relationships established in this informal collegiate setting among junior researchers are ones that may last a career (lifetime?!).

Eligibility: The New Researchers Conference is a meeting of recent Ph.D. recipients in Statistics and Probability. A new researcher is defined as anyone who has received a Ph.D. since 2000.

Those interested in attending the conference will be requested to submit the following information to the Committee: a letter of intent a curriculum vitae an abstract for a talk or poster. Electronic mail is preferred for abstract submission. Deadline for receipt of applications is February 15, 2005. Please apply promptly since the number of participants is limited. Priority will be given to first time participants. Women and minorities are encouraged to apply. Also, contingent on the availability of funds, support to defray travel and housing costs will be offered

August 17-19, 2005 MCP 2005, The 4th international conference on Multiple Comparison Procedures
Location: Shanghai, China.

Co-sponsored by ICSA to celebrate 50 years of Multiple Comparisons. Covering all topics related to multiple comparisons, conference details are being posted at the web site
http://www.stat.ohio-tate.edu/~mcp2005.
Participants can submit title and abstract via the web. Deadline of title/abstract submission is March 31, 2005.

Investigator and Postdoctoral Fellow Positions in Biostatistics and Bioinformatics

National Health Research Institutes (NHRI)
Taiwan, R.O.C.

The National Health Research Institutes (NHRI) is a rapidly growing non-profit organization supported by the Government of R.O.C. **The Division of Biostatistics and Bioinformatics** in the NHRI is seeking outstanding researchers for the positions at the levels of Assistant Investigator, Associate Investigator, and Investigator (equivalent to Assistant Professor, Associate Professor, and Professor in Universities). These are fully funded positions with opportunities for independent and collaborative research. Postdoctoral Fellow positions are also available. Candidates should have a Ph.D. or equivalent degree in **statistical science**, **epidemiology**, **computational biology**, **computer science** or related fields. Good skills in problem solving, interpersonal communication and coordination will be a plus.

The Division actively engages in NHRI intramural and extramural research design, data management and analysis, and commits to the advancement of biostatistics and bioinformatics research. Current research includes clinical trials, genetic studies and epidemiological studies etc. Bioinformatics Core Laboratory is established by the Division to facilitate genomic studies. Methodological research focuses on the topics, which have broad and valid biomedical applications. We are establishing a multi-disciplinary group to work together analyzing many interesting data in a variety of studies to elucidate health related scientific problems.

Application should include: A letter of intent, curriculum vitae with publication list, a brief research proposal, reprints of selected publications, and three reference letters sent directly to

Dr. Chao A. Hsiung, Director
Division of Biostatistics and Bioinformatics
National Health Research Institutes
128 Yen-Chiu-Yuan Road, Sec II
Taipei 115, Taiwan, R.O.C.
Tel: 886-2-2653-4401 ext. 7110
Fax: 886-2-2789-0253
E-mail: hsiung1@nhri.org.tw
NHRI web site - http://www.nhri.org.tw

Our Sincere Thanks!

The Editorial Team

As always, many good friends have taken time from their busy schedules to write for the Bulletin. Without their help, this issue of the Bulletin would be impossible.

We especially appreciate the generosity of Professor Xiru Chen to take time for Professor Zhang to conduct the interview. It is both time consuming and hard work to put the contents of the interview in print. This great contribution from Professor Zhang should never be under appreciated. In addition, I would like to thank Professor Dennis Lin for his coordination of this event. It provides a wonderful opportunity for us to know the progress of statistical development in China

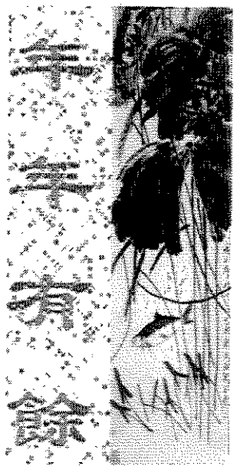
We would also like to thank Professor T.L. Lai for providing us the longest special feature article in the ICSA Bulletin's history. We always admire his insights and unlimited knowledge of various areas of statistics. His pioneer contribution in the statistical aspects of medical research will surely have great influence.

We would also like to express our thanks toward Dr. Hailiang Yang, and Professor Tsao for providing us with the local statistical activities in their respective regions. These efforts will greatly enhance the interactions between the statisticians around the world. We also thank Tamkang University and NHRI's support to advertise their career opportunities in our Bulletin.

The Committee of the 2005 Applied Statistics Symposium is busy setting up the stage for another successful meeting in June at Washington, D.C. The work requires unconditional commitment from all the members involved.

The authors of the contemporary statistical issues also deserve our special thanks. The topics discussed there continue to be one of our highlights in the Bulletin.

In addition to all the thanks, we would like to wish every reader and his or her family the happiest and healthy New Year.




鸛立鷄羣一可謂超然無侶矣
然進而觀於大海之鵬則眇然自小
又進而求之九霄之鳳則巍乎莫及
所以至人常若無若虛而盛德多不矜不伐也