BIOGRAPHICAL SKETCH

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NAME: Tze Leung Lai

eRA COMMONS USER NAME (credential, e.g., agency login): LAI.TZE

POSITION TITLE: Professor of Statistics

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Hong Kong University, Hong Kong	B.A.	1967	Mathematics
Columbia University, New York	M.A.	1970	Statistics
Columbia University, New York	Ph.D.	1971	Statistics

A. Personal Statement

I am Professor of Statistics and, by courtesy, of Health Research and Policy and of the Institute of Computational and Mathematical Engineering at Stanford University. I am also Co-director of the Biostatistics Core of the Stanford Cancer Institute and Center for Innovative Study Design at Stanford University School of Medicine. I have supervised 70 PhD theses and six postdoctoral trainees. I have published nearly 300 papers, many of which are in clinical trial design and analysis, population pharmacokinetics and pharmacodynamics, survival analysis, longitudinal data analysis, multiple endpoints, biomarkers, adaptive methods, sequential analysis and time series.

As Co-director of the Biostatistics Core of the Stanford Cancer Institute, the development and validation of biomarker-guided targeted therapies for cancer has been a major area of my research over the past few years. Moreover, several major advances and breakthroughs in innovative design and analysis of clinical trials have been made in the last three years. Examples of these are in the following:

1. Lai, TL, Lavori, PW and Shih, MC. Sequential design of Phase II-III cancer trials. Stat. Med. 2012, 31, 1944–1960. doi: 10.1002/sim.5346
2. Bartroff, J, Lai, TL and Narasimhan, B. A new approach to designing phase I-II cancer trials for cytotoxic chemotherapies. Stat. Med. 2014, 33, 2718–2735. doi: 10.1002/sim.6124
3. Lai, TL, Lavori, PW and Liao, OY. Adaptive choice of patient subgroup for comparing two treatments. Contemp. Clin. Trials 2014, 39, 191–200.
4. Lai, TL, Lavori, PW and Tsang, KW. Adaptive design of confirmatory clinical trials: Advances and challenges. Contemp. Clin. Trials 2015, in press.

B. Positions and Honors

Positions and Employment

1971–1974	Assistant Professor of Statistics, Columbia University
1974–1977	Associate Professor of Statistics, Columbia University
1977–1986	Professor of Statistics, Columbia University
1986–1987	Higgins Professor of Mathematical Statistics, Columbia University
1987–	Professor of Statistics, Stanford University
2001–2004	Chair, Department of Statistics, Stanford University
2005–	Co-director, Biostatistics Core, Stanford Cancer Institute
2005–	Director, Program in Financial Mathematics, Stanford University
2007–	Professor, by courtesy, of Health Research and Policy, Stanford University School of Medicine

2009 – Professor, by courtesy, Institute of Computational and Mathematical Engineering, Stanford University
2009 – Co-director, Center for Innovative Study Design, Stanford University School of Medicine

Other Experience and Professional Memberships

1977–1981 Research Collaborator, Brookhaven National Laboratory
1977–1987 Statistical Consultant, Pediatric Pulmonary Division, Columbia Presbyterian Medical Center
1989–1993 External Examiner, National University of Singapore
1991– External Assessor, Chinese University of Hong Kong
1992– Advisory Committee Member, Institute of Statistical Science, Academia Sinica
2002– Advisory Committee Member, National Health Research Institute (Taipei)
2003– Chair of Advisory Committee, School of Statistics, Morningside Center of Mathematics (Beijing)
2005– Data and Safety Monitoring Committee, Stanford University Cancer Center
2008– Member, Translational Oncology (formerly Molecular Therapeutics) Program, Stanford University Cancer Institute

Honors

1983 COPSS (Committee of Presidents of Statistical Societies) Award
1983 John Simon Guggenheim Fellowship
1994 Elected Member of Academia Sinica
1999 Center for Advanced Study in the Behavioral Sciences Fellowship
2005 Abraham Wald Prize in Sequential Analysis
2010 Pao-Lu Hsu Lecture in Statistics, Peking University
2012 Saw Swee Hock Lecture in Statistics, University of Hong Kong

C. Contribution to Science

1. An area in which I have been collaborating with other researchers at the Stanford Cancer Institute in the past four years is the development and validation of personalized therapies in Phase II trials and innovative Phase I cancer trials. Some representative papers are the following:
    a. Bartroff, J and Lai, TL. Incorporating individual and collective ethics into Phase I cancer trial designs. *Biometrics* 2011, **67**: 596–603. doi: 10.1111/j.1541-0420.2010.01471.x
    b. Lai, TL, Lavori, PW, Shih, MC and Sikic, B. Clinical trial designs for testing biomarker-based personalized therapies. *Clin. Trials J.* 2012, **9**: 141–154. doi: 10.1177/1740774512437252
    c. Lai, TL and Liao, OY. Efficient adaptive randomization and stopping rules in multi-arm clinical trials for testing a new treatment. *Sequential Anal.* 2012, **31**: 441–457. doi: 10.1080/07474946.2012.719433
    d. Lai, TL, Liao, OY and Kim, DW. Group sequential designs for developing and testing biomarker-guided personalized therapies in comparative effectiveness research. *Contem. Clin. Trials* 2013, **36**: 651–663. doi: 10.1016/j.cct.2013.08.007

2. I have made seminal contributions to population pharmacokinetics (PK) and pharmacodynamics (PD), to which I and my former Ph.D. students have introduced a novel method of fitting the population PK/PD model and using it to estimate the concentration versus time curve or the drug effects of a subject who has covariate information but sparse observations. We have also extended the method to generalized linear models for longitudinal data. Because of its computational tractability, our method allows flexible modeling of covariate effects by using regression splines and model selection procedures for knot and variable selection. Representative papers are:
    a. Lai, TL and Shih, M. Nonparametric estimation in nonlinear mixed effects models. Biometrika 2003, 90:1–13.
    b. Lai, TL and Shih, M. A hybrid estimator in nonlinear and generalized linear mixed effects models. *Biometrika* 2003, **90**:859–879.
    c. Lai, TL, Shih, M and Wong, SP. A new approach to modeling covariate effects and individualization in population pharmacokinetics-pharmacodynamics. *J. Pharmacok. Pharmacodynam.* 2006, **33**:49–74. doi:10.1007/s10928-005-9000-2

d. Lai, TL, Shih, M and Wong, SP. Flexible modeling via a hybrid estimation scheme in generalized mixed models for longitudinal data. *Biometrics* 2006, **62**:159–167. doi: 10.1111/j.1541-0420.2005.00391.x

3. I have made many fundamental contributions to sequential experimentation and analysis, which have recently found important applications to vaccine safety evaluation, public health surveillance, and group sequential clinical trials. Some representative papers are the following:
    a. Lai, TL. Sequential analysis: Some classical problems and new challenges (with discussion and rejoinder). *Statist. Sinica* 2001, **11**:303–408.
    b. Lai, TL and Li, W. Confidence intervals in group sequential trials with random group sizes and applications to survival analysis. *Biometrika* 2006, **93**:641–654. doi:10.1093/biomet/93.3.641
    c. Bartroff, J and Lai, TL. Approximate dynamic programming and its applications to the design of Phase I cancer trials. *Statist. Sci*. 2010, **25**:245–257. doi: 10.1214/10-STS317
    d. Shih, MC, Lai, TL, Heyse, JF and Chen, J. Sequential generalized likelihood ratio tests for vaccine safety evaluation. *Stat. Med*. 2010, **29**:2698–2708. doi: 10.1002/sim.4036

4. I have introduced novel approaches to multiple endpoints in clinical studies. The papers [4b] and [4c] are about efficacy and toxicity endpoints, while [4a] and [4b] introduce an innovative resampling approach to inference about secondary endpoints in a group sequential clinical trial whose stopping rule is based on the primary endpoint.
    a. Chuang, CS and Lai, TL. Hybrid resampling methods for confidence intervals (with discussion and rejoinder). *Statist. Sinica* 2000, **10**:1–50.
    b. Lai, TL. Sequential optimization under uncertainty. In *Modeling Uncertainty: An Examination of Stochastic Theory, Methods, and Applications* (M. Dror, P. L'Ecuyer, F. Szidarovszky, eds.) 2002, 35–55. Kluwer Academic Publishers, Norwell, MA.
    c. Bloch, DA, Lai, TL, Su, Z and Tubert-Bitter, P. A combined superiority and non-inferiority approach to multiple endpoints in clinical trials. *Stat. Med*. 2007, **26**:1193–1207. doi: 10.1002/sim.2611
    d. Lai, TL, Shih, MC and Su, Z. Tests and confidence intervals for secondary endpoints in sequential clinical trials. *Biometrika* 2009, **96**:903–915. doi:10.1093/biomet/asp063

5. I have made seminal contributions to innovative clinical trial designs in translational medicine and towards the new health care system following the 2010 Health Care Reform legislation. Some representative papers are the following:
    a. Lai, TL and Shih, MC. Power, sample size and adaptation considerations in the design of group sequential trials. *Biometrika* 2004, **91**:509–528.
    b. Lai, TL, Shih, MC and Zhu, G. Modified Haybittle-Peto group sequential tests for superiority and non-inferiority hypotheses in clinical trials. *Stat. Med*. 2006, **25**:1149–1167.
    c. Bartroff, J and Lai, TL. Efficient adaptive designs with mid-course sample size adjustment in clinical trials. *Stat. Med*. 2008, **27**:1593–1611. doi: 10.1002/sim.3201
    d. Lai, TL and Lavori, PW. Innovative clinical trial designs: Toward a 21st-century health care system. *Stat. Biosci.* **3**:145–168. doi: 10.1007/s12561-011-9042-5

D. Research Support

Ongoing Research Support

NCI 2P30 CA124435 Lai (Co-director, Biostatistics Core) 07.01.2010–06.30.2015
Cancer Institute Support Grant

NSF DMS 1407828 Lai (PI) 07.01.2014–06.30.2018
The past three years witnessed the beginning of a new era in financial markets and in the US health care system, following the health care and financial reform legislation of 2010. This era poses new challenges and opens up new opportunities for the field of Statistics. In addition, advances in high-performance computing and communication networks and in machine learning and statistical modeling of high-dimensional data have led to a new field called data science. A long-term objective of the proposed research is to develop innovative statistical methodologies and combine them with advances in data science for addressing challenges in

quantitative finance and health care, and resolving related fundamental problems in engineering and economics. In the past decade, spurred by applications to personalized strategies in medicine and electronic business, there has been great interest in contextual bandits; the proposed research is expected to develop a definitive contextual bandit theory. Applications to genomic-guided personalized cancer treatments and web-based recommender systems will also be explored.

Completed Research Support

NSF DMS 1106535 Lai (PI), Siegmund (Co-PI) 07.01.2011–12.31.2014
Statistical Methodology and Applications to Economics, Engineering and Genetics

An important objective of the proposed research is to develop statistical methods for gene mapping, i.e., the identification of genomic regions containing a gene (or genes) affecting a trait of interest in either humans or in experimental organisms. A closely related area of research is estimation and forecasting problems in time series models and stochastic dynamical systems whose parameters may change with time. The broader implications of the research include (i) direct applications in genetics, where mapping can be the first step towards better diagnostics or treatment of a disease or towards improving plant or animal stocks, in engineering and in finance, and (ii) training the next generation of scientists by involving graduate students in all phases of the research.