

# INSTITUTE FOR MATHEMATICS AND ITS APPLICATIONS

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## IMA NEWSLETTER # 253

August 1-31, 1997

1997 Summer Program

### STATISTICS IN THE HEALTH SCIENCES

See the Winter 1997 IMA Update for a full description of the Summer 1997 program.

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| <b>News and Notes</b> |
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| <p>IMA Summer Program:</p> |
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| <p><b>STATISTICS IN THE HEALTH SCIENCES</b></p> |
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| <p>July 7-August 22, 1997</p> |
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| <p>Organizers: Donald A. Berry, Seymour Geisser, Patricia Grambsch,<br/>Joel Greenhouse, Elizabeth Halloran, Nicholas Lange, Barry<br/>Margolin, Sandy Weisberg, Scott Zeger (Chair), and Marvin Zelen.</p> |
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### Improved IMA Home Page

The IMA has substantially improved its home page on the World-Wide Web, accessible through netscape or other web-reading applications at

<http://www.ima.umn.edu>.

The page is continually under construction. We invite comments or suggestions, which may be addressed to

[webmaster@ima.umn.edu](mailto:webmaster@ima.umn.edu).

In particular, we appreciate any information about World-Wide Web links appropriate to current and upcoming IMA programs.

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PARTICIPATING INSTITUTIONS: Centre National de la Recherche Scientifique, Consiglio Nazionale delle Ricerche, Georgia Institute of Technology, Indiana University, Iowa State University, Kent State University, Michigan State University, Northern Illinois University, Ohio State University, Pennsylvania State University, Purdue University, Seoul National University (RIM - GARC), Texas A&M University, University of Chicago, University of Cincinnati, University of Houston, University of Illinois (Chicago), University of Illinois (Urbana), University of Iowa, University of Kentucky, University of Manitoba, University of Maryland, University of Michigan, University of Minnesota, University of Notre Dame, University of Pittsburgh, University of Southern California, University of Wisconsin, Wayne State University.

PARTICIPATING CORPORATIONS: Bellcore, Eastman Kodak, EPRI, Ford, Fujitsu, General Motors, Honeywell, IBM, Lockheed Martin, Motorola, Siemens, 3M.

## Schedule for August 1–31, 1997

### IMA Summer Program: **STATISTICS IN THE HEALTH SCIENCES**

July 7–August 22, 1997

Organizers: Donald A. Berry, Seymour Geisser, Patricia Grambsch, Joel Greenhouse, Elizabeth Halloran, Nicholas Lange, Barry Margolin, Sandy Weisberg, Scott Zeger (Chair), and Marvin Zelen.

Many important contributions to health care have been made by statistical scientists. Examples include development of randomized-control-trial and case-control methods of investigations. Nearly every aspect of health research has statistical components. These components are sometimes well developed and sometimes not. Frequently, researchers from different disciplines develop their own approach to a statistical problem, but with little interaction among the various disciplines. The overall aim of the workshop is to bring together statisticians with other substantive scientific workers, who are working in health areas with theoretical and methodological statisticians, to discuss and explore current statistical methods in the health sciences and to develop new methods where needed. In view of the rapidly changing health-care environment, the time is ripe for such an interchange. There are five topics, one for each week of the program, with the exception of the Clinical Trials topic, which will take place over two weeks. The topics, dates and organizers are:

**Week 1: Genetics.** July 7–11 (Elizabeth Halloran, Seymour Geisser)

**Week 2: Imaging.** July 14–18 (Scott Zeger, Joel Greenhouse, Nick Lange)

**Week 3: Diagnosis and Prediction.** July 21–25 (Patricia Grambsch, Seymour Geisser)

**Weeks 4 & 5: Design & Analysis of Clinical Trials.** July 28–Aug. 8 (Donald Berry, Marvin Zelen)

**Week 6: Statistics and Epidemiology: Environment and Health.** August 18–22 (Joel Greenhouse, Elizabeth Halloran, Marvin Zelen, Barry Margolin)

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### Weeks 4 & 5: Design & Analysis of Clinical Trials. July 28–Aug. 8

**Organizers: Donald Berry, Marvin Zelen**

Clinical investigations remain the single most important medical tool to evaluate and compare various therapies. This includes design and analysis for drug and vaccine development, and for evaluation of the efficacy and safety of therapeutic agents and vaccines. The issues involved include early stopping (interim analysis), censored missing data, problems of compliance, competing trials, intermediate endpoints, surrogate markers and univariate and multivariate survival analysis. Among the issues of interest are: the design of clinical investigations beginning with an understanding of drug mechanisms through pharmacokinetics/dynamics studies, and the assessment of drug safety and efficiency (*i.e.*, the design of Phase I, III, IV studies). We are also interested in the design of prevention and vaccine trials. A particularly challenging problem is the design of trials with multivariate endpoints.

**Monday, July 28**

**Talks today are in Seminar Room Vincent Hall 570**

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| 8:45 am | <b>Registration and Coffee</b>            | IMA Lounge Vincent Hall 502                |
| 9:15 am | <b>Welcome and Orientation</b>            | A. Friedman, R. Gulliver, D. Berry         |
| 9:45 am | <b>Marvin Zelen</b><br>Harvard University | The Theory and Practice of Clinical Trials |

*Abstract:* This lecture will discuss some of the important issues associated with the theory and practice of clinical trials. The lecture will consist of seven parts, i.e. early history, background, strategy of experimentation, informed consent and its ramifications, compliance and its effect on bias and efficiency, double randomized consent design and ethical issues.

The early history will discuss the work of James Linde who carried out his classic studies on scurvy in 1747. However, the prophylactic effect of lemon juice was discovered by the East India Company almost 150 years before. In the 19th century, many American physicians journeyed to France to study with the famous French physician, P.C.A. Louis. He wrote that one must “count” in order to learn about the benefits of therapy. However, counting is not easy. He wrote that “unfortunately it requires more labor and time than the most distinguished members of our profession can dedicate to it.”

One question which dominates the transfer of clinical investigation outcomes to the clinic is what proportion of therapies shown to be positive from a clinical trial are actually positive. It is shown that this proportion is not as high as one generally believes. Our conclusion is that there are large numbers of false positive therapies in current clinical use.

Clinical trials carried out in the U.S. require affirmative patient consent. As a result, the conclusions from a trial only apply to those patients who would give consent. Very often the consent process divides patients into prognostic groups where those who decline to give consent have poorer prognosis than those patients who do consent. As a result the conclusions of a trial may not strictly apply to the population of people with disease.

Compliance is a key factor in a well conducted clinical trial. However, lack of compliance may induce biases and result in very low efficiencies. This is especially important in prevention trials which attempt to change behavior, e.g. smoking, drinking, dieting.

Many physicians have been reluctant to participate in randomized clinical trials because they feel that the patient-physician relationship may be compromised. In an attempt to increase physician participation in randomized trials, a new way of designing randomized trials was introduced several years ago. These trials are called “randomized consent” or “pre-randomized” designs. These will be discussed from both practical and ethical points of view.

Finally, clinical trials have generated new ethical concerns. Several neglected ethical issues will be discussed which require more public discussion.

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| 10:45 am | <b>Coffee Break</b>                       | IMA Lounge Vincent Hall 502  |
| 11:15 am | <b>John Simes</b><br>University of Sydney | Design strategies for handling several similar randomised trials addressing common treatment questions |

*Abstract:* Often a single large scale trial will be undertaken at the same time as other trials addressing similar treatment questions. This raises important issues in planning individual trials as well as how to make maximum use of the evidence from all such trials. Two problems are discussed. The first deals with the issue of how an ongoing trial is affected by the results from other trials which provide some evidence of treatment effect. A model is proposed for continuing the trial provided i) the specific questions being addressed in the trial are still open ii) patients are given the opportunity to receive treatment where appropriate iii) revised power calculations, based on some patients opting to have treatment, indicate that the trial is still viable.

The second issue deals with the opportunity of combining the results of similar individual trials to address questions for which there is inadequate power within the individual studies: such as mortality effects or treatment effects within particular subgroups. A meta-analysis of these trials is limited by the retrospective nature of the analysis, where decisions about which trials, patients groups, treatments and outcomes to include and what specific analyses to undertake may be based on knowledge of the results from specific trials included in the

analysis. Prospective meta-analysis (PM) provides a model to avoid such bias. PM prespecifies the objectives, treatments, patient groups and outcomes clearly in a protocol prior to the results of any trial being known. This model requires prior agreement of each individual trial group to be included in the combined analysis and has similar methodological strengths to intergroup trials. Approaches to both of these issues will be illustrated.

2:00 pm            **Richard Simon**                            Bayesian Analysis of Active Control Clinical Trials  
National Cancer Institute

*Abstract:* We consider the design and analysis of active controlled clinical trials; that is, clinical trials comparing an experimental treatment  $E$  to a control treatment  $C$  considered to be effective. Direct comparison of  $E$  to placebo  $P$ , or no treatment, is often medically contraindicated. Establishing the effectiveness of  $E$  is usually based on demonstrating that  $E$  is not “significantly” worse than  $C$ . We propose an alternative approach. We define an additive model of treatment effect and place prior distributions on parameters representing the outcome of patients receiving placebo ( $\alpha$ ), and on the effects of  $C$  and  $E$  relative to placebo ( $\beta$  and  $\gamma$  respectively). Using normal prior distributions, we show that the posterior distribution of the parameters, given normally distributed data from the active controlled trial, is multivariate normal. Consequently, the posterior probability that  $E$  is superior to  $P$  can be easily calculated. The posterior probability that  $E$  is at least  $k\%$  as good as  $C$  and that  $C$  is more effective than  $P$  is also easily calculated for any  $k$  (e. g. 50% or 80%). We also derive approximations for use with binary or right-censored response. In general we recommend that non-informative priors be used for  $\alpha$  and  $\gamma$  and that a random-effects meta-analysis of randomized clinical trials comparing  $P$  to  $C$  be used to provide a prior for  $\beta$ .

4:00 pm            **IMA Tea (and more!)**                            Vincent Hall 502 (The IMA Lounge)

A variety of appetizers and beverages will be served.

**Tuesday, July 29**

**Talks today are in Seminar Room Vincent Hall 570**

9:15 am            **Coffee**    IMA Lounge Vincent Hall 502

9:30 am            **Roger J. Lewis**                                    A Bayesian Approach to the Analysis of a Random-  
UCLA School of Medicine                            ized Prehospital Clinical Trial

*Abstract:* Over the last several years, we have been conducting an ongoing randomized comparison of two methods paramedics use to help critically-ill and injured children breathe as they are brought to the hospital. This study, which involves critically-ill and injured children treated by paramedics in Los Angeles and Orange Counties, California, was designed using a group sequential decision-theoretic Bayesian clinical trial design. The group sequential clinical trial design, and its implementation, will be discussed.

Because critically-ill and injured children form a highly heterogenous population, there is significant clinical interest in subgroup analysis in this study. A simplified Bayesian approach to this subgroup analysis will be described. This approach involves the use of an expert panel to obtain prior distribution functions for each of the clinically important subgroups. Emphasis will be placed on the importance of the effective communication of the information from the clinical trial to clinicians and prehospital care providers, rather than on statistical sophistication.

10:30 am            **Coffee Break**    IMA Lounge Vincent Hall 502

11:00 am            **Donald A. Berry**                                    Using Historical Controls, Decision Making, and  
Duke University    Adaptive Designs in Clinical Trials

*Abstract:* I will address three aspects of designing clinical trials: (1) Using historical controls in addition to or in lieu of patients assigned to control in a randomized trial. I compare hierarchical modeling with modifying likelihoods with subjective assessment of prior distributions. There are circumstances in which each of these



For substances, in which the efficacy/safety are directly link to the pharmacodynamic and therefore the pharmacokinetics of the substance, combining these evaluations might lead to considerable gain in knowledge. This knowledge might be extremely useful for the dose schedule selection for achieving the required efficacy. An example in a phase II trial in which 153 seasonal allergic rhinitis patients were treated with an i.v. application of an anti-IgE compound will be use to illustrate the evaluation of efficacy with respect to pharmaco-dynamic and pharmacokinetics. This information will be use for dose schedule recommendation of the phase III study using a SC route of administration. Population modeling approach will be used, issues concerning parametrization, model and covariate selection will be discussed.

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| 2:00 pm | <b>Discussion Session</b>  | Stangl, Racine-Poon <i>inter alia</i> |
| 5:00 pm | <b>Workshop Taco Party</b> | Courtyard behind Vincent Hall         |

### Friday, August 1

#### Talks today are in Seminar Room Vincent Hall 570

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| 9:15 am  | <b>Coffee</b>  | IMA Lounge Vincent Hall 502                            |
| 9:30 am  | <b>Stan Young</b><br>Glaxo Wellcome Inc.                   | The analysis of clinical trials with multiple outcomes |
| 10:30 am | <b>Coffee Break</b>  | IMA Lounge Vincent Hall 502                            |
| 11:00 am | <b>Ross L. Prentice</b><br>Hutchinson Cancer Research Ctr. | Analysis of Multivariate Failure Time Data             |

*Abstract:* Methods for assessing dependency between pairs of censored failure time variates will be described. These include estimators of parameters in semiparametric models, including Clayton's constant relative-risk model, and estimators of nonparametric dependency measures, including an average relative risk measure and a finite region version of Kendall's tau. Nonparametric estimators of the bivariate survivor function provide a basic tool for such assessment, as well as for a range of other multivariate failure time data analysis topics. A modification of the bivariate survivor function estimator of Dabrowska that removes negative mass and appears to improve estimation efficiency will be presented, along with preliminary work on a corresponding nonparametric maximum likelihood estimator. Regression generalizations of these various statistics will be briefly mentioned, along with genetic epidemiologic motivations.

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| 2:00 pm | <b>Discussion Session</b> | Young, Prentice <i>inter alia</i> |
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### Monday, August 4

#### Talks today are in Seminar Room Vincent Hall 570

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| 9:15 am | <b>Coffee</b>                                    | IMA Lounge Vincent Hall 502             |
| 9:30 am | <b>M. Elizabeth Halloran</b><br>Emory University | Special Issues in Vaccine Field Studies |

*Abstract:* Although vaccine field studies conform in many ways to the paradigm of clinical trials of treatments, they also have their own characteristics. First, the vaccine can be evaluated for both how it reduces susceptibility,  $VE_S$ , and how it reduces infectiousness,  $VE_I$ , as well as how it slows progression,  $VE_P$ . Secondly, the transmission probability or secondary attack rate is a parameter that can be used to estimate both  $VE_I$  and  $VE_S$ . Thirdly, vaccination can have indirect as well as direct effects in populations, so that even unvaccinated people benefit from widespread vaccination. Studies can be designed to evaluate both individual and population level effects

of vaccination. Fourthly, the various VE parameters can be thought of as a hierarchy depending on how much information about the contact and transmission process is used for their estimation. This led to the idea of efficient design of vaccine studies by combining sets of study participants with differing levels of exposure to infection data using missing data and errors-in-variables methods. We present the design and data analysis methods for these different special characteristics of vaccine studies.

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| 10:30 am | <b>Coffee Break</b>                                 | IMA Lounge Vincent Hall 502                      |
| 11:00 am | <b>L. J. Wei</b><br>Harvard School of Public Health | Play the Winner for Phase II/III Clinical Trials |

*Abstract:* In comparing two treatments under a typical sequential clinical trial setting, a 50-50 randomization design generates reliable data for making efficient inferences about the treatment difference for the benefit of patients in the general population. However, if the treatment difference is large and the endpoint of the study is potentially fatal, it does not seem appropriate to sacrifice a large number of study patients who are assigned to the inferior arm. An adaptive design is a data-dependent treatment allocation rule that sequentially uses accumulating information about the treatment difference during the trial to modify the allocation rule for new study patients. In this talk, we utilize real trials from AIDS and cancer to illustrate the advantage of using adaptive designs. Specifically we show that, with adaptive designs, the loss of power for testing the equality of two treatments is negligible. Moreover, the study patients do not have to pay a handsome price for the benefit of future patients. We also propose multi-stage adaptive rules to relax the administrative burden of implementing the study and to handle continuous response variables, such as the failure time in survival analysis.

This is joint work with Q. Yao.

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| 2:00 pm | <b>Discussion Session</b> | Halloran, Wei <i>inter alia</i> |
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IMA Special Lecture in Vincent Hall 570:

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| 2:00 pm | <b>Greg Baker</b><br>Ohio State University | On the Nature of Singularity Formation During Vortex Sheet Motion |
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*Abstract:* Vortex sheets are asymptotic models for the motion of infinitely thin shear layers in slightly viscous liquids. However, there is overwhelming evidence that they form curvature singularities in finite time. For two dimensional motion, D.W. Moore's pioneering work gives rise to the interpretation that branch point singularities in the sheet location are present in the complex plane of the circulation variable. These singularities move towards and reach the real axis in finite time. A question arises on the origin of such singularities when the initial data is analytic. By continuing the evolution equations into the complex plane, recent work describes how these singularities form immediately at certain points in the complex plane. Further, they are shown to be 3/2-power singularities. Work in progress indicates such singularities are also present in axi-symmetric flow.

This is joint work with Stephen Cowley and Saleh Tanveer.

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| 4:00 pm | <b>IMA Tea (and more!)</b> | Vincent Hall 502 (The IMA Lounge) |
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A variety of appetizers and beverages will be served.

**Tuesday, August 5**

**Talks today are in Seminar Room Vincent Hall 570**

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| 9:15 am | <b>Coffee</b> | IMA Lounge Vincent Hall 502 |
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| 9:30 am | <b>Peter F. Thall</b><br>M.D. Anderson Cancer Center | A Strategy for Dose-Finding and Safety Monitoring<br>Based on Efficacy and Adverse Outcomes in Phase<br>I/II Clinical Trials |
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*Abstract:* We propose a design strategy for single-arm clinical trials with goals (1) to find a dose of an experimental treatment satisfying both safety and efficacy requirements, (2) treat a sufficient number of patients to estimate the rates of these events at the selected dose with a given reliability, and (3) stop the trial early if it is likely that no dose is both safe and efficacious. Patient outcome is characterized by a trinary ordinal variable accounting for both efficacy and toxicity. We use Bayesian criteria to generate decision rules while relying on frequentist criteria obtained via simulation to determine a design parameterization with good operating characteristics. The strategy is illustrated by application to a bone marrow transplantation trial and a biologic agent trial.

This is joint work with Kathy E. Russell.

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| 10:30 am | <b>Coffee Break</b>                               | IMA Lounge Vincent Hall 502  |
| 11:00 am | <b>Thomas A. Louis</b><br>University of Minnesota | Data and decision based prior partitions<br>with application to monitoring clinical trials |

*Abstract:* Unlike classical approaches, Bayesian methods enable expert opinion and objective information to augment data from an experiment, with the potential for more efficient designs and analysis. These advantages come at the expense of more sophisticated computing (to elicit priors and perform the analysis), and the methodology's apparent lack of objectivity relative to a frequentist approach. Robust Bayesian methods that perturb the prior or assess inferences for a class of priors have been developed to address the objectivity issue.

This presentation explores an alternate approach based on a partial characterization of the class of priors that, for a given data set, lead to a specific decision such as rejecting a point null hypothesis. These characterizations are intended to complement other Bayesian and frequentist data summaries. Non-parametric approaches based on moments and percentiles of the prior, and methods for parametric families such as the Gaussian and exponential with conjugate priors have been developed. The approach will be illustrated using monitoring data from a recent AIDS clinical trial.

Joint IMA/School of Mathematics Seminar in Murphy Hall 130

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| 11:30 am | <b>Giovanni Galdi</b><br>Univ. of Ferrara | Steady Navier-Stokes Flow Past a Self-Propelled<br>Body |
| 2:00 pm  | <b>Discussion Session</b>                 | Thall, Louis <i>inter alia</i>                          |

**Wednesday, August 6**

**Talks today are in Seminar Room Vincent Hall 570**

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| 9:15 am | <b>Coffee</b>                               | IMA Lounge Vincent Hall 502                   |
| 9:30 am | <b>Stephen L. George</b><br>Duke University | Surrogate Endpoints in Cancer Clinical Trials |

*Abstract:* The complete evaluation of a therapeutic intervention for many diseases such as AIDS and cancer requires lengthy and costly follow-ups of patients both for long-term benefit (e.g., survival) and late-occurring adverse events. In recent years, attention has been given to investigation of potential "surrogate" endpoints for these "true" endpoints. The potential benefits in terms of earlier results and less expensive studies are obvious. But there are significant risks as well. There are examples in which the use of surrogate endpoints produced dangerously misleading results. This presentation will explore some of the statistical issues in evaluating

surrogate markers. Examples will focus primarily on cancer clinical trials, including prevention, screening, and therapeutic trials.

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| 10:30 am | <b>Coffee Break</b>                      | IMA Lounge Vincent Hall 502                      |
| 11:00 am | <b>Stan Young</b><br>Glaxo Wellcome Inc. | Recursive Partitioning Analysis of Clinical Data |

*Abstract:* Relating medical outcomes to covariates, designed or happenstantial, is a complex task. There is a need for power to detect effects and for the effects found to be “real” i.e. reproducible. We examine recursive partitioning as a method of analysis, exploratory and definitive. Several methods are reviewed, several data sets are examined using RP, and issues are raised concerning false positive questions, sample size, and prospective design of studies where analysis is to be RP.

This is joint work with Alok Krishen and Doug Hawkins.

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|---------|-----------------------------|---------------------------------|
| 2:00 pm | <b>Discussion Session</b>   | George, Young <i>inter alia</i> |
| 5:00 pm | <b>Workshop Pizza Party</b> | Back Patio of Vincent Hall      |

#### Thursday, August 7

##### Talks today are in Seminar Room Vincent Hall 570

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| 9:15 am | <b>Coffee</b>                                     | IMA Lounge Vincent Hall 502                                     |
| 9:30 am | <b>Ping Hu</b><br>Harvard School of Public Health | Planning Clinical Trials to Evaluate Early Detection Programmes |

*Abstract:* The lack of statistical theory for the planning of early detection trials has resulted in current trials being sub-optimal. We develop probability models that address three characteristics of early detection trials: (i) the optimal time of analysis and length of follow-up; (ii) the optimal spacing between examinations; and (iii) the planning of trials where the numbers of examinations versus sample size are balanced for fixed costs. The optimization criterion is to maximize the power of the statistical test for comparing mortality. The theory will be utilized to evaluate the benefit of early detection of disease combined with treatment as well as to review current breast trials.

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| 10:30 am | <b>Coffee Break</b>                                   | IMA Lounge Vincent Hall 502                                   |
| 11:00 am | <b>Ori Davidov</b><br>Hutchinson Cancer Research Ctr. | Mathematical Models in the Design of Cancer Prevention Trials |

*Abstract:* Reducing cancer incidence has been a major goal of the medical and public health communities over the last decades. Broad scale preventive clinical trials (PCT’s) relating cancer prevention to chemoprevention, dietary changes and behavioral modification are being planned or are currently in progress for breast, prostate, and lung cancer among others. Currently studies are planned using relative risk regression. We introduce alternatives such as semi Markov and multistep stochastic models. Thus relevant biological processes can be incorporated and the utility and feasibility of prevention trials better understood.

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| 2:00 pm | <b>Discussion Session</b> | Hu, Davidov <i>inter alia</i> |
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#### Friday, August 8

IMA Special Lecture in Vincent Hall 570:

11:00 am

**Hong Wang**  
University of South Carolina

On Numerical Methods for Advection-Diffusion-  
Reaction Equations  
and Their Comparisons

*Abstract:* Advection-diffusion-reaction equations arise in the modeling of fluid dynamics, enhanced oil recovery, contaminant transport in groundwater, fluid mechanics, atmospheric modeling, and many other important applications. These equations are characterized by solutions with moving fronts and present serious difficulties in numerical simulation. Space-centered finite difference and finite element methods usually generate numerical solutions with non-physical undershoot and overshoot about the true solutions. While upwinding methods can eliminate these oscillations, they introduce considerable numerical dispersion and yield numerical solutions with serious over-damping. Many specialized methods have been developed to overcome these difficulties, such as the Petrov-Galerkin method, the flux-corrected transport method, the streamline diffusion finite element method, the continuous and discontinuous Galerkin method, the monotonic upstream-centered scheme for conservation laws (MUSCL) and the essentially non-oscillatory scheme (ENO), as well as different characteristic methods.

We present an Eulerian-Lagrangian localized adjoint method (ELLAM) for advection-diffusion-reaction equations with various combinations of inflow and outflow Dirichlet, Neumann, and flux boundary conditions. The ELLAM formalism provides a systematic framework for implementation of general boundary conditions, leading to mass-conservative numerical schemes. The scheme allows large time steps in the simulation without loss of accuracy, thus significantly improves the efficiency of the simulation. Numerical results will be presented to observe the performance of the ELLAM scheme and the numerical methods mentioned above.

**Monday, August 11**

**IMA Industrial Postdoc Seminar**

The seminar will meet from 1:00 – 4:00 pm today in Vincent Hall 570. The format of the seminar is:

1. Presentation of projects and problems from industry (Honeywell, Lockheed Martin and Kodak) on which the industrial postdocs are working.
2. Informal suggestions and discussion among the participants.

The seminar is directed by Avner Friedman and Walter Littman. Visitors who plan to attend are requested to inform Dr. Friedman.

**Tuesday, August 12**

**Wednesday, August 13**

**Thursday, August 14**

**Friday, August 15**

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| <b>Week 6: Statistics and Epidemiology: Environment and Health.</b> |
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**August 18–22**

**Organizers: Joel Greenhouse, Elizabeth Halloran, Marvin Zelen, Barry Margolin**

The objective of Week 6 is to examine the special analytic problems associated with observational studies in drawing associations between exposures and disease outcomes. Not only are epidemiologic studies observational, but often the quality of the data is poor. Some of these problems include measurement error, informative missingness, aggregate data used for defining individual risks, the use of monitoring and surveillance data and the use of geographic information systems (GIS) for spatial mapping. The leading question is whether it is possible to draw inferences about causal effects of exposures on disease outcomes in epidemiologic studies.

The realization of the connection between health and the environment is only a recent phenomenon. It reflects advances in the science of measurement and the development of statistical techniques capable of dealing with complex data. It is a further purpose of this workshop to discuss several case studies of environmental problems relating to health, including the role of small changes in the magnitude of air pollution on mortality.

**Monday, August 18**

**Talks today are in Seminar Room Vincent Hall 570**

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|---------|--|---|
| 8:45 am | <b>Registration and Coffee</b>               | IMA Lounge Vincent Hall 502   |
| 9:15 am | <b>Welcome and Orientation</b>               | A. Friedman, R. Gulliver, B. Margolin   |
| 9:30 am | <b>Noel Cressie</b><br>Iowa State University | Bayesian Inference for Disease Incidence Rates at Aggregated and Point Levels |

*Abstract:* Hierarchical probability models for disease-incidence rates can be used to obtain the joint posterior distribution for an entire set of small-area rates while taking into account the spatial nature of the data. Maps of disease incidence rates will differ depending on whether optimal ensemble estimation is the goal or special emphasis is placed on other functions, such as extreme values. The fit of the hierarchical model should also be assessed; methodology using posterior predictive checks will be presented. An important inferential question is that of determining whether a high disease-incidence rate is larger than would be expected by chance under the model.

It is natural to build models at the aggregate level because typically disease-incidence data are available only over small areas. However, it is important that such models be consistent with more individual-level mechanisms. By postulating mechanisms at the individual level and then aggregating up to the small-area level, we build hierarchical statistical models that allow us to incorporate medical, epidemiological, and demographic knowledge about the disease.

This talk presents joint research with Hal Stern.

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| 10:30 am | <b>Coffee Break</b>                            | IMA Lounge Vincent Hall 502   |
| 11:00 am | <b>Lance Waller</b><br>University of Minnesota | A Case Study in Spatial Analysis of Hospital Discharge Data: Childhood Asthma and Environmental Pollution in San Diego County, CA |

*Abstract:* The State of California Office of Statewide Health Planning and Development collects hospital discharge diagnoses annually in California. For this study, we address discharges associated with childhood (ages 0-14) asthma (ICD code 493) hospitalizations in San Diego County for 1990. Of particular interest is the potential exacerbating effect of exposure to automobile exhaust. Using traffic density as a surrogate for exposure to automobile pollutants, we obtain data on street locations and traffic flow for the county. These data are linked to ZIP code level socio-economic characteristics from the U.S. Census using a geographic information system (GIS). We conduct exploratory spatial analyses for patterns in the asthma data. Based on the exploratory results

we fit generalized linear mixed models to assess effects of putative risk factors. The models allow residual spatial correlations, which we use to assess model fit and motivate model improvements.

This is joint work with Erin Conlon, Li Zhu, Paul English and Rusty Scalf.

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|---------|---|---|
| 2:00 pm | <b>Bradley P. Carlin</b><br>University of Minnesota | Hierarchical modeling in geographic information systems: Population interpolation over incompatible zones |
|---------|---|---|

*Abstract:* When inference is desired regarding some attribute of a particular geographic region, it often happens that data are not directly available for that region. However, it may be that data are available over the same general area, but reported according to a different set of regional boundaries. Recently, powerful computer programs called geographic information systems (GIS's) have enabled the simultaneous display of such "misaligned" data sets, but these systems address only the descriptive needs of the user, leaving the inferential goal unmet. In this paper we describe a hierarchical Bayes approach, implemented via Markov chain Monte Carlo methods, which provides a natural solution to this problem through its ability to sensibly combine information from several sources of data and available prior information. After presenting a simple idealized example to illustrate the method, we apply it to a data set on leukemia rates in Tompkins County, New York, wherein we use census tract-level covariate information to interpolate disease counts given only aggregate (block group-level) summaries. We display our results graphically using both statistical (*S-plus*) and GIS (*ArcInfo*) software packages. The approach emerges as flexible, accurate, and suggestive of promising related methods for spatial smoothing of underlying relative risks.

This is joint work with Andrew S. Mugglin.

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| 4:00 pm | <b>IMA Tea (and more!)</b> | Vincent Hall 502 (The IMA Lounge) |
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A variety of appetizers and beverages will be served.

## Tuesday, August 19

### Talks today are in Seminar Room Vincent Hall 570

|         |  |                             |
|---------|--|-----------------------------|
| 9:15 am | <b>Coffee</b>                            | IMA Lounge Vincent Hall 502 |
| 9:30 am | <b>Carl Morris</b><br>Harvard University | Fitting hierarchical models |

*Abstract:* Statisticians, epidemiologists, and other data analysts are noticing more often when their data have several levels of variation, and so they must choose and fit a multi-level model. "Fitting" here refers both to deciding on an appropriate model that fits the data, and deciding on a fitting procedure that correctly analyzes the assumed model. In the first case, the model's assumptions are checked with the data. The exchangeability assumption, made for the distributions at the second level of variation, are special to hierarchical modeling and perhaps the most critical. In the second case, especially when only a few units are considered together, these models are complex and approximations are aided very little by large-sample asymptotics. Then significant biases can occur, even from fitting with commonly-used fitting computation methods (e.g. maximum likelihood). Using fully Bayesian procedures overcomes some problems, but their repeated-sampling properties depend on the prior distribution or reference prior used for the population parameters, and often have not been evaluated for the specific distribution used. We discuss these and other related issues with some theoretical and practical examples.

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| 10:30 am | <b>Coffee Break</b>                                    | IMA Lounge Vincent Hall 502                            |
| 11:00 am | <b>Judea Pearl</b><br>Univ. of California, Los Angeles | Graphs and Counterfactuals in Epidemiological Analysis |

*Abstract:* It is well known that any method of drawing cause-effect inferences from nonexperimental studies must rely on subject-matter assumptions in one form or another. This paper compares two such forms: causal

graphs and Rubin’s potential-response model. Using a new formalization of causal graphs, we show that the two approaches above are logically equivalent: the unit-response function in Rubin’s model is a derived property of causal graphs, the rules that govern counterfactual variables in Rubin’s model are theorems in the causal-graph formulation and, moreover, the graphical representation introduces no extraneous features beyond those used in counterfactual analysis. This implies that researchers can articulate subject-matter information in the friendly language of graphs, use the graphs as a convenient inference-aiding device, and be assured that all inferences match those derivable by the more cumbersome method of potential-response analysis. We will demonstrate the practical use of causal graphs in solving the problem of confounder identification: Given qualitative understanding of causal relationships among variables in the environment, some of which are unmeasurable, find a subset of observed covariates that, if adjusted for, would yield consistent estimate of the causal effect of exposure on disease.

References:

Pearl, J., “Causal diagrams for experimental research, (with discussion),” *Biometrika* **82**(4), 669–710, 1995.  
 Galles, D. & Pearl, J., “An Axiomatic Characterization of Causal Counterfactuals,” UCLA Computer Science Department, Technical Report (R-250), June 1997.

Available on: [http://bayes.cs.ucla.edu/jp\\_home.html](http://bayes.cs.ucla.edu/jp_home.html)

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|---------|---|---|
| 2:00 pm | <b>Mark van der Laan</b><br>Univ. of California, Berkeley | Dealing with informative censoring and high dimensional data structures |
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*Abstract:* We propose a methodology for testing a treatment effect when the outcome variables (e.g. survival times) are subject to informative censoring and the data structure for every subject is high-dimensional. In particular, we deal with current status data, interval censored data, right-censored data, and bivariate right-censored data, where we allow for each of these data structures the presence of time-dependent covariates.

**Wednesday, August 20**

**Talks today are in Seminar Room Vincent Hall 570**

|         |   |  |
|---------|---|--|
| 9:15 am | <b>Coffee</b>                                   | IMA Lounge Vincent Hall 502                                  |
| 9:30 am | <b>Norm Breslow</b><br>University of Washington | Design and Analysis of Two-Phase Studies with Binary Outcome |

*Abstract:* The two-phase stratified sampling design, with selection into the second phase (validation) sample dependent on both outcome and covariate factors observed for everyone, offers an efficient and cost effective alternative to designs in current use. In a motivating example from the National Wilms Tumor Study, two different strategies are used to sample “cases” (treatment failures) and “controls” for purposes of central pathology review: (i) standard case-control sampling, with controls drawn at random from the treatment successes; and (ii) balanced case-control sampling, with all patients of “unfavorable” histology according to the institutional pathologist included in the case-control sample. Three methods of analysis are considered: (i) Horvitz-Thompson (weighted likelihood) estimation; (ii) pseudo-likelihood; and (iii) nonparametric maximum likelihood. The performance of the six design-analysis strategies is investigated by comparing the estimated regression coefficients with estimates from a standard logistic regression analysis of the complete data. This shows clearly the advantages of balanced over standard case-control sampling and of maximum likelihood over the other analysis methods.

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| 10:30 am | <b>Coffee Break</b>  | IMA Lounge Vincent Hall 502  |
| 11:00 am | <b>Gregory T. Golm</b><br>Rollins School, Emory University | Semiparametric Models for Mismeasured Exposure Information in Vaccine Trials |

*Abstract:* Exposure-to-infection information is important for estimating vaccine efficacy, but it is difficult to collect and inherently prone to missingness and mismeasurement. It is therefore not feasible to collect good exposure information on all participants in a large vaccine trial. We discuss study designs which collect detailed exposure information for only a small subset of trial participants, while collecting crude exposure information on all participants, and treat estimation of vaccine efficacy in the missing data/measurement error framework. We demonstrate with the example of an HIV vaccine trial the improvements in bias and efficiency when combining the different levels of exposure information to estimate vaccine efficacy for reducing both susceptibility and infectiousness. We compare the performance of recently developed semiparametric missing data methods of Pepe and Fleming and Robins, Hsieh, and Newey.

This is joint work with Elizabeth Halloran and Ira Longini.

|         |   |   |
|---------|---|---|
| 2:00 pm | <b>Raymond J. Carroll</b><br>Texas A&M University | Combining Disparate Data in a Risk Assessment of Acute Inhalation Exposures |
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*Abstract:* We will present our work on marginal (classical and robust) and random effects analysis of a risk assessment to acute inhalation exposures of PERC. The data come from many small studies, and include observations on mice, rats and humans. Difficulties in defining endpoints are described. An Splus program was written to implement the methods.

This is joint work with Douglas G. Simpson, Mixge Xie and Daniel Guth.

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| 5:00 pm | <b>Workshop Buffet</b><br>Location to be announced |
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**Thursday, August 21**

**Talks today are in Seminar Room Vincent Hall 570**

|         |   |   |
|---------|---|---|
| 9:15 am | <b>Coffee</b>                           | IMA Lounge Vincent Hall 502   |
| 9:30 am | <b>David Dunson</b><br>Emory University | Semiparametric resampling methods for imputing clustered observations |

*Abstract:* Data are often clustered in correlated groups in medical studies. Endpoints of interest may include the cluster size and/or one or more binary outcomes on each unit within a cluster. In vaccine and toxicology applications the effect of an exposure on the cluster size can be assumed to be isotonic. A variety of resampling methods are proposed for imputing the potential cluster sizes in the absence of exposure under this assumption. Standard models can then be fit to estimate a dose-response relationship or to test for an overall toxic effect. These methods are applied to data sets and are evaluated through simulation studies. Fully nonparametric and Bayesian alternatives are proposed.

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|------------|---|-----------------------------|
| 10:30 am   | <b>Coffee Break</b>                                     | IMA Lounge Vincent Hall 502 |
| 11:00 am   | <b>Joel Schwartz</b><br>Harvard School of Public Health | To be announced             |
| 12:00-1:00 | <b>Workshop Discussion Session</b>                      |                             |

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**Friday, August 22**

**Monday, August 25**

**Tuesday, August 26**

Wednesday, August 27

Thursday, August 28

Friday, August 29

|                                 |
|---------------------------------|
| <b>CURRENT IMA PARTICIPANTS</b> |
|---------------------------------|

POSTDOCTORAL MEMBERS FOR 1996-97 PROGRAM YEAR

| NAME               | PREVIOUS INSTITUTION              |
|--------------------|-----------------------------------|
| GOBBERT, MATTHIAS  | Arizona State University          |
| LOTOTSKY, SERGEY   | University of Southern California |
| MALIASSOV, SERGUEI | Texas A&M University              |
| NGUYEN, BRIAN      | University of Michigan            |
| NIE, QING          | Ohio State University             |
| SARKAR, SANHITA    | University of Minnesota           |
| SUCHOMEL, BRIAN    | University of Wyoming             |
| YANG, DAOQI        | Wayne State University            |

POSTDOCTORAL MEMBERSHIPS IN INDUSTRIAL MATHEMATICS FOR 1996-97

| NAME               | PREVIOUS INSTITUTION     | INDUSTRIAL AFFILIATION |
|--------------------|--------------------------|------------------------|
| CHAWLA, SANJAY     | University of Tennessee  | Honeywell              |
| KOURITZIN, MICHAEL | Carleton University      | Lockheed Martin        |
| LOPEZ, GILBERTO    | Northwestern University  | Eastman Kodak          |
| WANG, LEI          | University of Washington | Honeywell              |

VISITORS IN RESIDENCE (as of 7/10)

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|                     |  |                    |
|---------------------|--|--------------------|
| BAKER, GREGORY      | Ohio State University                      | AUG 3 - 7          |
| BERRY, DON          | Duke University                            | JUL 27 - AUG 5     |
| BRESLOW, NORMAN     | University of Washington                   | AUG 17 - 22        |
| CAMPBELL, GREGORY   | FDA Center f. Devices & Radiol. Health     | JUL 27 - AUG 8     |
| CARLIN, BRADLEY P.  | University of Minnesota                    | AUG 17 - 22        |
| CARROLL, RAYMOND J. | Texas A&M University                       | AUG 17 - 22        |
| CHALONER, KATHRYN   | University of Minnesota                    | JUL 28 - AUG 8     |
| COCKBURN, BERNARDO  | University of Minnesota                    | SEP 1 - AUG 31     |
| CRESSIE, NOEL       | Iowa State University                      | AUG 17 - 20        |
| DAVIDOV, ORI        | Fred Hutchinson Cancer Research Center     | JUL 28 - AUG 8     |
| DEVINE, OWEN J.     | Center for Disease Control & Prevention    | AUG 17 - 22        |
| DIXON, DENNIS       | National Institutes of Health              | JUL 27 - AUG 8     |
| DORR, DAVID         | Washington University -St. Louis           | JUL 6 - AUG 22     |
| DUNSON, DAVID B.    | Rollins Sch. of Public Health, Emory Univ. | AUG 17 - 22        |
| FRIEDMAN, AVNER     | Institute for Mathematics                  | SEP 1 - AUG 31     |
| GEORGE, STEVE       | Duke University                            | AUG 4 - 6          |
| GOLM, GREGORY       | Rollins Sch. of Public Health-Emory        | AUG 17 - 22        |
| GU, CHI             | Washington University                      | JUL 27 - AUG 9     |
| GULLIVER, ROBERT    | Institute for Mathematics                  | SEP 1 - AUG 31     |
| HALLORAN, ELIZABETH | Emory University                           | AUG 3 - 8, 17 - 22 |
| HEJHAL, DENNIS      | University of Minnesota                    | SEP 1 - AUG 31     |
| HORN, PAUL S.       | University of Cincinnati                   | JUL 27 - AUG 1     |
| HU, PING            | Harvard School of Public Health            | JUL 28 - AUG 8     |
| KAPLAN, DANIEL      | Macalester College                         | JUL 7 - AUG 14     |

|                      |  |                             |
|----------------------|--|-----------------------------|
| LAWSON, ANDREW       | University of Abertay Dundee           | AUG 17 - 24                 |
| LITTMAN, WALTER      | University of Minnesota                | SEP 1 - AUG 31              |
| LOUIS, THOMAS        | University of Minnesota                | JUL 28 - AUG 8              |
| LOWENGRUB, JOHN      | University of Minnesota                | SEP 1 - AUG 31              |
| LUSKIN, MITCHELL     | University of Minnesota                | SEP 1 - AUG 31              |
| MALEC, DON           | FDA Center f. Devices & Radiol. Health | JUL 27 - AUG 8              |
| MARGOLIN, BARRY      | Univ. of North Carolina                | JUL 27 - AUG 8, AUG 17 - 22 |
| MORRIS, CARL         | Harvard University                     | AUG 17 - 22                 |
| OEHLERT, GARY        | University of Minnesota                | AUG 17 - 22                 |
| PARMIGIANI, GIOVANNI | Duke University                        | JUL 20 - AUG 8              |
| PEARL, JUDEA         | Univ. of California-Los Angeles        | AUG 17 - 22                 |
| PRENTICE, ROSS       | University of Washington               | JUL 30 - AUG 1              |
| RACINE-POONE, AMY    | Novartis                               | JUL 27 - AUG 1              |
| ROBINS, JAMES M.     | Harvard University                     | AUG 17 - 22                 |
| ROSENBAUM, PAUL      | University of Pennsylvania             | AUG 17 - 22                 |
| SCHWARTZ, JOEL       | Harvard School of Public Health        | AUG 17 - 22                 |
| SELL, GEORGE         | University of Minnesota                | SEP 1 - AUG 31              |
| SIMES, JOHN          | University of Sydney                   | JUL 28 - AUG 8              |
| SPIRITES, PETER      | Carnegie Mellon University             | AUG 17 - 22                 |
| STANGL, DALENE       | Duke University                        | JUL 27 - AUG 5              |
| ŠVERÁK, VLADIMIR     | University of Minnesota                | SEP 1 - AUG 31              |
| THALL, PETER         | U. of Texas Anderson Cancer Center     | AUG 2 - 6                   |
| THOMAS, NEAL         | University of North Carolina           | AUG 17 - 22                 |
| VAN DER LAAN, MARK   | Univ. of California-Berkeley           | AUG 17 - 22                 |
| WALLER, LANCE        | University of Minnesota                | AUG 17 - 22                 |
| WEI, L.J.            | Harvard University                     | JUL 28 - AUG 8              |
| WEISBERG, SANDY      | University of Minnesota                | JUL 7 - AUG 29              |
| WILLIAMS, VANESSA    | Glaxo Wellcome                         | AUG 17 - 22                 |
| YIN, GEORGE          | Wayne State University                 | AUG 17 - 22                 |
| YOST, MICHAEL        | University of Washington- Seattle      | AUG 17 - 22                 |
| YOUNG, STANLEY       | Glaxo, Inc.                            | JUL 28 - AUG 8              |
| ZELEN, MARVIN        | Harvard School of Public Health        | JUL 23 - AUG 8              |