6TH CONFERENCE OF THE EASTERN MEDITERRANEAN REGION OF THE INTERNATIONAL BIOMETRIC SOCIETY

BOOK OF ABSTRACTS

HERSONISSOS - CRETE
8-12 MAY 2011
BOOK OF ABSTRACTS

SIXTH CONFERENCE OF THE EASTERN MEDITERRANEAN REGION OF THE INTERNATIONAL BIOMETRIC SOCIETY (EMR-IBS)

HERSONISSOS, CRETE, 8-12 MAY 2011
Preface

We are very glad to welcome you at Hersonissos, Crete at the heart of the Mediterranean sea, for the 6th conference of the Eastern Mediterranean Region of the International Biometric Society (EMR-IBS).

The 6th EMR-IBS conference coincides with the 10-year anniversary of the formation of the EMR region of IBS, which includes the following countries: Cyprus, Egypt, Greece, Israel, Jordan, Palestinian National Authority, Turkey, Saudi Arabia and recently, Bulgaria. This is the last of a very successful series of conferences started in Athens, Greece in 2001, followed by Antalya, Turkey in 2003, Corfu, Greece in 2005, Eilat, Israel in 2007 and finally Istanbul, Turkey in 2009.

The conference is dedicated to the memory of Steve Lagakos who, in his efforts of promoting Biostatistical Science in the Region, has been a great supporter of EMR, participating actively in all of the Regional conferences. In 2005, he gave a full-day workshop on Clinical Trials to medical professionals to provide the funding to support student participation in the 3rd EMR conference. He had the vision of making the region an educational center for young Biostatisticians and Clinical Trialists. He collaborated with Postgraduate Studies Programs where he served as a Visiting Instructor for many years and he co-founded in 2007, Frontier Science Foundation-Hellas (FSF-H), in Athens, Greece where he served as a member of its Board of Directors.

Frontier Science & Technology Research Foundation (FSTRF) sponsors the Lagakos Memorial Lectures, with invited talks by world renowned statisticians to be presented throughout the meeting. Frontier Science Foundation-Hellas (FSF-H) is supporting the participation of young researchers in his memory, providing 3 student awards to students with the best submitted abstracts. These talks will be presented at a special session on the last day of the conference.

A complete list of all the abstracts of the papers to be presented in the conference can be found in this book. A detailed index of all authors can be found at the end to facilitate easy search.

We hope that you will enjoy the 6th EMR-IBS Conference honoring the memory of Steve Lagakos and celebrating the 10 year anniversary of EMR.

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on behalf of the LOC and SC.
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Keynote Lecture
One Man’s Meat: Nutrition Biomarkers in Chronic Disease Prevention Research

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Abstract. Variation between individuals both in their dietary intake and in their biological responses to such diet makes nutritional epidemiology a fascinating topic. However, difficulties in accurately quantifying dietary intake through self-reporting make it difficult to study hypothesized associations between diet and disease. One response to these challenges has been the emergence of biomarkers for dietary intake. I review this development and the uses of such biomarkers in chronic disease prevention research. I focus on several different roles that biomarkers can play in this endeavor, including assessing compliance and mediation analysis in prevention trials, calibration of self-report instruments, adjustment of estimated relative risks for dietary measurement error in observational studies, and enhancing the statistical power of such studies. Examples are provided from the Women’s Health Initiative dietary intervention trial, the Observing Protein and Energy study and the Carotenoids in Eye Disease Study.

Keywords

biomarkers, cohort studies, nutrition, measurement error, prevention trials

References


Lagakos Memorial Lectures
Clinical Trials and the Growth of Regulations

David L. DeMets

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Abstract. The randomized clinical trial has been the primary research method for evaluating new drugs, biologics, devices, procedures and behavioral modifications. Industry conducts many randomized clinical trials to evaluate their new products or novel application of existing products. These products must be approved for clinical use by regulatory agencies of countries in which the product will be marketed. The regulatory bodies have produced regulations that guide the design, conduct, analysis and presentation of these trials, especially trials which are going to be used for the registration or approval process. There is no single set of guidelines but among them are those of the US Food and Drug Administration and the International Conference on Harmonization (ICH). Trials are increasingly being conducted worldwide and so requirements may differ across countries or regions. While the principles of these guidance documents are generally consistent with fundamentals of clinical trials, their interpretation and application have become more complex, time consuming and expensive over the past decade. We will discuss some of these practices and whether they lead to better trials. Recent experience suggests that the current trends cannot be sustained.

Plenary Talk
Confronting the Challenges of Subgroup Analyses in Clinical Trials

Richard D. Gelber
Dana-Farber Cancer Institute, Harvard School of Public Health, Harvard Medical School and Frontier Science and Technology Research Foundation, Boston, MA, USA

Abstract. Proper conduct and interpretation of subgroup analyses in clinical trials are challenging.[1] Such analyses are subject to unacceptably high levels of false-positive and false-negative error rates. If improperly interpreted, they can lead to erroneous conclusions that can have substantial detrimental effects on patient care, either denying effective treatment to some patients, or encouraging use of ineffective treatments for others. Steve Lagakos publicized these concerns, but also recognized the importance of subgroup analyses to provide guidance for care of individual patients and to generate hypotheses to be tested in future clinical investigations. He wrote in 2006, [2] "When subgroup analyses are properly conducted, presentation of their results can be informative, . . . avoiding any presentation of subgroup analyses because of their history of being over interpreted is a steep price to pay for a problem that can be remedied by more responsible analysis and reporting."

In this presentation I will review challenges of subgroup analyses using examples from clinical trials evaluating adjuvant therapies for breast cancer. Steve Lagakos served as a member of the Data and Safety Monitoring Committees for these trials and his wise counsel contributed substantially to their successful and ethical completion. Interpretation of subgroup analyses based on dichotomizing a continuous measure such as age or a biomarker represents a specific challenge. The Subpopulation Treatment Effect Pattern Plot (STEPP) method was developed to explore treatment effect heterogeneity as a function of a covariate measured on a continuous scale.[3-6] STEPP has been applied in a variety of settings to highlight patterns of treatment effect differences based on the biological diversity of the underlying disease process and therapeutic response.[7,8] Examples will be presented to stimulate discussion.

References

Building Global Capacity in Statistics

Ronald E. LaPorte, Ph.D. for the Supercourse team

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Abstract. World wide there are over 300 times more clinicians than there are statistics. There are 20 times more morticians there are those trained in statistics. In many developing countries there are no statistical training programs. This is at a time when there has been an explosion of data. There is a critical need for more individuals to be trained in statistics in developed and developing countries alike. Ideally we would like to build more masters and Ph.D. programs in developing countries. However, this is not practical as there typically is not the expertise for teaching, and in these days the costs are prohibitive. We have taken a different approach for work for development in statistics and other areas. Our goal is not to produce Ph.D.s in statistics, but rather to build awareness and interest in statistics for students. We want to double the training in statistics world wide in the next 5 years.

In most medical, and nursing schools world wide in 4-6 year training students might have 15 minutes training in statistics. The reason that there is a paucity is that few faculty can teach about statistics. We are changing this. Our approach is simple, we have a network of over 50,000 faculty interested in global health and prevention from 174 countries. From this network we have collected 4800 top quality lectures, 75 from Nobel Prize winners. We make the lectures available in a free open source library (www.pitt.edu/ super1/). We feed the lectures back to the faculty and the world, and they are then able to teach in areas that may not be their primary areas of expertise, as they have top quality, up to date lectures. We have already doubled the training of global health in the world. There are 31 different languages represented in the supercourse. In the past year our lectures have taught over 6 million people. We have distributed these lectures to all medical, public health and nursing schools in the world.

We propose to build a statistical supercourse where we collect the top lectures of statistics and make these available for free. We currently have about 30 statistical and research design lectures available. We give all the credit for the lectures to the authors, as we are like an art gallery, and the lectures are like the art. A statistical Supercourse would help build awareness of statistics to many 1000s more students than are available now.

Panel Discussion
An Overview of Screening Programs for the Early Diagnosis of Chronic Diseases: Issues and Problems

Sandra Lee
Dana-Farber Cancer Institute and Harvard School of Public Health, Department of Biostatistics and Computational Biology

Abstract. The screening of asymptomatic individuals for chronic disease is a public health initiative that is rapidly growing. This is especially true in cancer where there are expanding early detection programs in breast, cervical, colorectal, lung, prostate and stomach cancers. The basic idea motivating the screening asymptomatic populations is that diagnosing the disease early before it becomes symptomatic may result in better prognosis. We have developed stochastic models to describe the early detection process. Our model can project various outcomes of screening programs, including the mortality reduction associated with screening programs. Our theoretical results have been applied to the problems arise in breast cancer screening. In this talk, the stochastic model and model assumptions will be presented. In addition, the following topics and examples will be discussed: i) periodic vs. risk-based screening, ii) mammogram screening in younger women (ages between 40-49), iii) overdiagnosis from breast cancer screening, iv) contribution of mammogram screening in the US breast cancer mortality reduction between 1975-2000 and v) collaborations with the U.S. Preventive Services Task Force in updating the U.S. mammogram guideline in 2009. The last two examples are noteworthy as the modeling result had a significant impact in understanding the role of breast cancer screening in the U.S. population.
Inference on Treatment Effects from a Randomized Clinical Trial in the Presence of Premature Treatment Discontinuation: The SYNERGY Trial

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Abstract. The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa inhibitors (SYNERGY) trial was a randomized, open-label, multi-center clinical trial comparing two anticoagulant drugs (enoxaparin and unfractionated heparin, UFH) on the basis of various time-to-event endpoints. In contrast to those of other studies of these agents, the primary, intent-to-treat analysis did not find sufficient evidence of a difference, leading to speculation that premature discontinuation of the study agents by some subjects might have attenuated the treatment effect. As is the case in such trials, some subjects discontinued (stopped or switched) their assigned treatment prematurely, either because occurrence of an adverse event or other condition under which discontinuation was mandated by the protocol or due to other reasons, e.g., switching to the other treatment at his/her provider’s discretion (with more subjects switching from enoxaparin to UFH than vice versa). In this situation, interest often focuses on “the difference in survival distributions had no subject discontinued his/her assigned treatment,” inference on which is often attempted via standard analyses where event/censoring times for subjects discontinuing assigned treatment are artificially censored at the time of discontinuation. However, this and other common ad hoc approaches may not yield reliable information because they are not based on a formal definition of the treatment effect of interest. We use SYNERGY as a context in which to describe how such an effect may be conceptualized properly and to present a statistical framework in which it may be identified, which leads naturally to the use of inverse probability weighted methods. This is joint work with Min Zhang (University of Michigan), Marie Davidian (North Carolina State University), and Karen Pieper and Ken Mahaffey (Duke Clinical Research Institute)

Keywords

inverse probability weighting, potential outcomes, proportional hazards model
Student Awards
Augmented Cross-Sectional Studies with Abbreviated Follow-up for Estimating HIV Incidence

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Abstract. Cross-sectional HIV incidence estimation based on a sensitive and less-sensitive test offers great advantages over the traditional cohort study. However, its use has been limited due to concerns about the false negative rate, reflecting the phenomenon that some subjects may remain negative permanently on the less-sensitive test. Wang and Lagakos (2010) propose an augmented cross-sectional design which provides one way to estimate the false-negative rate and subsequently incorporate this information in the cross-sectional incidence estimator. In an augmented cross-sectional study, subjects who test negative on the less-sensitive test in the cross-sectional survey are followed forward for transition into the nonrecent state, at which time they would test positive on the less-sensitive test. However, considerable uncertainty exists regarding the appropriate length of follow-up and the false negative rate. In this paper, we assess the impact of varying follow-up time on the resulting incidence estimators from an augmented cross-sectional study, evaluate the robustness of these estimators to assumptions about the existence and the size of the subpopulation who will remain negative permanently, and propose a new estimator based on abbreviated follow-up time (AF). Compared to the original estimator, the AF estimator allows shorter follow-up time and does not require estimation of the mean window period, defined as the average time between detectability of HIV infection with the sensitive and less-sensitive tests. It is shown to perform well in a wide range of settings. We discuss when the AF estimator would be expected to perform well and offer design considerations for an augmented cross-sectional study with abbreviated follow-up.

Keywords

augmented, cross-sectional studies; false negative; incidence estimators
Nonparametric Estimation of Distribution Functions in Measurement Errors Models

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Abstract. Many practical problems are related to the estimation of distribution functions when data contains measurement errors. For example, consider the estimation of the prevalence of a disease which is determined by some underlying biomarker, measured with error, having value greater than some known constant. Another example is the estimation of the area under the receiver operating characteristic curve which is widely used in biostatistical studies. These two examples deal with some functionals of the distribution function.

In this work we consider the problem of nonparametric estimation of some smooth functionals in measurement errors models. We study minimax complexity of this problem when the unknown distribution has a density belonging to the Sobolev class, and the error density is ordinary smooth or supersmooth. We develop rate optimal estimators based on direct inversion of the empirical characteristic function.

For the problem of estimating a distribution function we also propose an adaptive version of the estimator and illustrate its superiority with respect to other methods both theoretically and through simulations. A real example of estimating hypertension prevalence is discussed. Extensions to other important estimation problems are also studied.

Keywords

adaptive estimator, deconvolution, error in variables, prevalence

This work is based on the PhD thesis of the author done under the supervision of Prof. Alexander Goldenshluger and Prof. Benjamin Reiser.
Modelling Health Surveillance Data via a Bivariate INAR(1) Process

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Abstract. Non-negative integer-valued time series are often encountered in many different scientific fields, usually in the form of counts of events at consecutive time points. Many representative examples of such data can be found in epidemiology. Due to their frequent occurrence, a wide variety of models appropriate for treating such data have been proposed in the literature (Grunwald et al., 2000). Among the most popular are the INteger-valued AutoRegressive (INAR) models (McKenzie, 1985; Al-Osh and Alzaid, 1987). In this work, we extend the simple INAR(1) model to the 2-dimensional space. In this way we define a bivariate INAR(1) process (BINAR(1)), we examine its marginal properties and proposed the method of maximum likelihood for the estimation of its unknown parameters. Extensions to incorporate covariate information are discussed while emphasis is placed on models with bivariate Poisson and bivariate negative binomial innovations. Other distributional assumptions allowing for overdispersion and negative correlation are also briefly considered.

To motivate the model we use the example of syndromic surveillance during Athens 2004 Olympic Games and investigate the potential of lower effectiveness of the system during weekends compared to weekdays.

Keywords

counts, BINAR, Poisson, negative binomial, syndromic surveillance

References


Invited papers
Dependence Calibration in Conditional Copulas: A Nonparametric Approach

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Abstract. The study of dependence between random variables is a mainstay of statistics. In many cases, the strength of dependence between two or more random variables varies according to the values of a measured covariate. We develop inference for this type of variation via a conditional copula model in which the copula is parametric and its parameter varies as the covariate. We propose a nonparametric procedure based on local likelihood to estimate the functional relationship between the copula parameter and the covariate, derive the asymptotic properties of the proposed estimator and outline the construction of pointwise confidence intervals. We also contribute a novel conditional copula selection method based on cross-validated prediction errors and a generalized likelihood ratio-type test to determine if the copula parameter varies significantly. We derive the asymptotic null distribution of the formal test. Using a subset of the Matched Multiple Birth dataset, we demonstrate the performance of these procedures via analysis of gestational age-specific twin birth weights.

Keywords

conditional copula, covariate adjustment, generalized likelihood ratio test, local likelihood
Unbalanced and Partial Group Sequential Methods for Normal Responses in Clinical Trials

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Abstract. Group sequential methods for a two treatment clinical trial with normal responses are discussed. First we consider the case where the sample sizes for two treatments are possibly unequal between the two groups due to an unequal randomization. Then we discuss group sequential design in the context of a historical-control study, that is, under the partial sequential sampling scheme, in which the samples on one treatment, say control, are available at the outset, and the samples on the other treatment, say experimental, are obtained in the group sequential way. We discuss the cases of known and unknown variance for unbalanced and partial group sequential set up. All the procedures are discussed with simulation studies.

Keywords
clinical trials, group sequential methods, multivariate t distribution, partial sequential sampling, type I error spending function

References

Improved Estimation of Survival Probabilities from Two-phase Stratified Samples

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Abstract. A standard problem in clinical epidemiology is the estimation of 5 year survival probabilities for cancer patients using information on age and stage of disease at diagnosis and the histology and molecular characteristics of the tumor. Cost considerations may limit the number of stored tissue samples that are utilized in expensive bioassays. Stratified sampling is then useful to identify the most informative tissue samples to send to bioassay, assuming that demographic, clinical and outcome data are already available for all subjects. Prediction of survival or other outcomes at designated times after diagnosis is generally accomplished using parametric or semiparametric models for failure time data, in particular, the Cox proportional hazards model.

The standard method for estimating Euclidean parameters in (semi)parametric models from stratified samples is Horvitz-Thompson weighting of the estimating equations, using as weights the inverse sampling probabilities. In previous work we have shown how adjustment of the weights, either by their calibration to known totals of auxiliary variables or their estimation using these same variables, can markedly improve the efficiency of estimation of Euclidean parameters, e.g., of hazard ratios in the Cox model. By separating likelihood calculations, based on the model, from those on weak convergence of the inverse probability weighted empirical process, based on the sampling design with or without adjustment, our general results apply to a variety of (semi)parametric models. Here we apply these results to joint estimation of Euclidean and infinite dimensional parameters, in particular, to prediction of survival outcomes for individual patients using the hazard ratios and baseline hazard of the Cox model.

References

More Robust Doubly Robust Estimators

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Abstract. Considerable recent interest has focused on doubly robust estimators for a population mean outcome in the presence of incomplete data, which involve models for both the propensity score and the regression of outcome on covariates. These estimators have the appealing property that they are consistent for the true population mean even if one of the outcome regression or propensity score models, but not both, is misspecified. However, the usual doubly robust estimator may yield severely biased inferences if neither of these models is correctly specified and can exhibit nonnegligible bias if the estimated propensity score is close to zero for some observations. We propose alternative doubly robust estimators that achieve comparable or improved performance relative to existing methods. This is joint work with Weihua Cao (US Food and Drug Administration) and Anastasios Tsiatis North Carolina State University).

Keywords
causal inference, missing at random, no unmeasured confounders, outcome regression
Order Restricted Inference for Multivariate Binary Data with Applications

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Abstract. In many applications such as toxicology, epidemiology, genetics and the social sciences, researchers collect multivariate binary response data under two or more, naturally ordered experimental conditions. In such situations one is often interested in using all binary outcomes simultaneously to detect order related trends among the experimental conditions. We show that the problem of determining dose related trends can be formulated as a multivariate stochastic ordering problem. We develop a methodology for the analysis of $K \geq 2$ multivariate binary distributions which are subject to such order restrictions. Our simulation studies indicate that order restricted estimators of the population proportions are often more efficient in terms of their mean squared error than the unconstrained estimators. The reduction in total mean squared error can be as much as 40%. We propose a test that incorporates the ordering of all binary outcomes simultaneously. This test is shown to be much more powerful than the unrestricted Hotelling $T^2$ type procedure. We also compared the proposed test to procedures which combine univariate tests for order. In particular we studied several union intersection type tests and a Bonferroni based test. Our simulations suggest that the proposed method competes well with these alternatives. The gain in power is often substantial. The proposed methodology is illustrated by applying it to a two year rodent cancer bioassay data obtained from the US National Toxicology Program (NTP).

Keywords

binary data, dose response studies, stochastic order relations, order restricted statistical inference
Abstract. We show a novel approach for k-FWER control which does not involve any correction, but only testing the hypotheses along a (possibly data-driven) order until a suitable number of p-values are found above the uncorrected $\alpha$ level. p-values can arise from any linear model in a parametric or non parametric setting. The approach is not only very simple and computationally undemanding, but also the data-driven order enhances power when the sample size is small (and also when $k$ and/or the number of tests is large). The procedure retains the error control under independence and weak dependence of p-values (see Farcomeni, 2007 and Clarke and Hall, 2009). As an alternative, a simple correction is proposed in order to retain the control under any dependence. We illustrate the method on an original study about gene discovery in multiple sclerosis, in which we were involved a small number of couples of twins, discordant by disease.

The paper is now published on Biometrics (Finos and Farcomeni 2010) and the methods are implemented in an R package (someKfwer), freely available on CRAN.

Keywords
data driven order, gene discovery, multiple sclerosis, multiple testing

References

Comparative Effectiveness Research: A Methodologic Introduction

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Abstract. Comparative Effectiveness Research (CER) is an initiative with wide ranging implications for biomedical research and health care policy. The term "CER" refers to a body of research that generates and synthesizes evidence on the comparison of benefits and harms of alternative methods to prevent, diagnose, treat, and monitor clinical conditions, or to improve the delivery of care. The evidence from Comparative Effectiveness Research is intended to support clinical and policy decision making at both the individual and the population level. The mandate of CER places a premium on the study of outcomes that are of primary relevance to patients and on the derivation of conclusions that can inform individual patient choices.

The broad scope of CER requires a wide array of methodological approaches. CER research may include both randomized and observational primary studies as well as research synthesis. In this presentation we will discuss the research questions addressed by CER and some of the statistical challenges they present.
Use of Composite Endpoints in Cardiovascular Device Trials involving Coronary Stents

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Abstract. Composite endpoints (CE) are nowadays used commonly as primary endpoint to assess the efficacy of a new treatment. It is sometimes unclear, and often controversial, which endpoint should be used in randomized clinical trials. For instance, in cardiovascular device trials involving coronary stents the often rare events of cardiovascular death and myocardial infarction are combined with more common events such as target lesion revascularization (TLR), target vessel revascularization (TVR) or non cardiovascular death. Although these events are combined with the aim to increase the statistical power of the study, adding less specific components might in fact lead to loss of power to detect the true treatment differences. In addition, improvement in the composite does not necessarily mean an improved survival. In other occasions, the usefulness of a CE relies in combining outcomes to have a better description of the disease process. Very often CEs are chosen for their potential for statistical efficiency and as a way of dealing with the issues of multiple testing and competing risks. In cardiovascular trials, the use of a CE is furthermore intricate due to the relative importance to patients of the different components as well as the magnitude of the effect of treatment across the component endpoints. Gómez and Lagakos (2011) developed a statistical methodology to derive guidelines for deciding whether to expand a study primary endpoint from $E_1$ (cardiovascular death and myocardial infarction, say) to the composite of $E_1$ and a secondary endpoint $E_2$ (TLR, say). Their method considers the asymptotic relative efficiency (ARE) of a logrank test for comparing treatment groups with respect to $E_1$ versus the composite endpoint of $E_1$ or $E_2$. The ARE depends on the marginal distributions of the times until $E_1$ and $E_2$, the correlation between these times, the treatment group differences with respect to $E_1$ and $E_2$, and the pattern and amount of censoring. The Gómez and Lagakos method is illustrated on two case studies. A set of recommendations is provided to obtain more efficient results in the area of coronary stents.

Keywords

Asymptotic Relative Efficiency; Composite outcome; Logrank test; Statistical Power

References


GÓMEZ and LAGAKOS (2011). Statistical considerations when using a composite endpoint for comparing treatment groups (submitted)
Treatment Noncompliance in Studies of Adjuvant Chemotherapy for Breast Cancer

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Abstract. The Trial Assigning Individualized Options for Treatment (TAILORx) uses Genomic Health’s Oncotype DX21 gene Recurrence Score (RS) assay to select adjuvant treatment for hormone receptor positive, node negative breast cancer. This assay was developed to predict recurrence risk (Paik et al, 2003) and retrospective analyses suggest RS may predict whether patients will benefit from chemotherapy (Paik et al, 2006). In TAILORx, patients with an RS < 11 are assigned to receive hormonal therapy (HT) only, patients with an RS > 25 are assigned to receive HT plus chemotherapy and patients with RS in range 11-25 are randomized to HT alone or HT plus chemotherapy. Accrual to TAILORx was completed in 2010, with 11,233 patients screened for RS evaluation and 6,907 patients with RS 11-25 randomized. Approximately 7% of the patients assigned to HT alone have received chemotherapy and 17% of the patients assigned to receive chemotherapy have refused it. There is substantial variation in treatment preference over the range of recurrence scores, and based on prior retrospective data, it is expected that the magnitude of the treatment effect may also vary with RS. Methods for accounting for this noncompliance in the design and analysis will be discussed and examples of noncompliance in other breast cancer studies will be presented.

Keywords

noncompliance, breast cancer, recurrence score

References

Estimation of Sensitivity of Chest X-ray and Cancer Preclinical Sojourn Time for Lung Cancer Screening Trials

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Abstract. The effectiveness of cancer screening depends crucially on two elements: the preclinical sojourn time (that is, the duration of the preclinical screen-detectable period) and the sensitivity of the screening test. Chest x-ray has historically been employed most frequently as the major screening test for lung cancer. Little is known about the accuracy of Chest x-ray in community practice.

To investigate this issue, one possibility is to use the available methods in prior literature. However, these methods first have largely concentrated on breast cancer screenings and second are assumed 100%-exact. It is clear that the data from most cancer screening trials do not support a zero false positive rate. Therefore, it would be interesting to generalize these commonly used methods by considering specificity also as a parameter and to estimate mean sojourn time/mean lead time, sensitivity and specificity simultaneously. It would be also interesting to demonstrate whether the existing methods used in breast cancer screening could be used in lung cancer screening. New method is applied to the data from the lung component of PLCO cancer screening trial and Yunnan Tin Miners Lung Cancer study in China.

Keywords
sojourn time, lead time, sensitivity, specificity, chest x-ray, lung cancer

References
Inference under Biased Sampling with Application to Infection Data

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Abstract. Selection bias is a general term for observed data having a different (biased) law than that of the target population. Correction of selection bias requires understanding and appropriate modelling of the biasing mechanism. A common and very important example of selection bias arises in cross-sectional designs in which data are collected on individuals who are available at a given place and time window; estimation methods for the lifetime distribution function are well developed under the assumption of steady state. In this talk, I review basic results in the analysis of data obtained in cross-sectional designs and discuss different aspects of the steady state assumption. I then discuss inference under cross-sectional designs for a population that can be joined in fixed and known time points. I demonstrate different ideas using several data sets collected by the Israeli Ministry of Health.

Part of the work is joint with Yosi Rinott, Rebecca Betensky, Ronen Fluss, Laurence Freedman, and the Department of Health Services and Research, the Ministry of Health, Israel.

Keywords
cumulative incidence, prevalence, truncation, weighted analysis
Issues in ROC Surface Analysis with an Application to Externally Validated Cognition in Parkinson Disease Screening

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Abstract. The diagnostic accuracy of the Montreal Cognitive Assessment (MoCA) has been established recently for screening externally validated cognition in Parkinson’s disease (PD) (Dalrymple-Alford et al, 2010). Patients were classified as having either normal cognition (PD-N), mild cognitive impairment (PD-MCI), or dementia (PD-D). ROC curve methodology has been used to assess discrimination between two adjacent classes and the Youden index has been employed for cut-off point selection. ROC surface methodology has also been used for the assessment of the simultaneous discrimination of the three classes. Recently, Nakas et al (2010) proposed a generalization of the Youden index for the assessment of accuracy and cut-off point selection in simultaneous discrimination of three classes. In this work, we examine properties of the generalized Youden index and compare two- vs. three-class classification accuracy approaches when screening for cognition status in PD.

Keywords

ROC analysis, Youden index, K-S statistic, Montreal cognitive assessment

References


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Formulation of Recommendation Domains for Sugarcane Varieties: Using Modified Stability Analysis and Best Linear Unbiased Predictor

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Abstract. This paper discusses two alternative statistical procedures, the modified stability analysis (MSA) and the best linear unbiased predictor (BLUP), that are effective in the formulation of recommendation domains for sugarcane varieties grown across ten sites in two Southern African countries (South Africa and Swaziland). The procedures are illustrated using yield data on fourteen sugarcane varieties not all grown in all the sites and in the same year. Furthermore, harvesting was done at different stages of ratoons, hence complicating the analysis. Modified stability analysis explicitly incorporates variation in field management, soils and climatic conditions and in the process enables evaluation of the performance of each variety relative to each site. The best linear unbiased predictor analysis takes into consideration factors that are fixed and factors that are random. The two approaches help scientists evaluate responses to treatments and partition sites into recommendation domains. The South African Sugar Association Research Institute (SASRI) and Swaziland Sugar Association Technical Services (SSATS) are continually extending outgrower services to new growing areas. Evaluation of commercial varieties across a range of sites is conducted with a view to drawing recommendation domains to growers for different agro climatic conditions and management practices. The current climatic conditions and socio-economic factors demand for development of high yielding varieties that utilise the available resources more efficiently. By formulating recommendation domains for these varieties, we respond to this demand. We demonstrate the process of the analysis, discuss the findings and highlight the challenges encountered. We conclude that no single analysis can handle this type of data and therefore advocate analysis done on stages.

Keywords

fixed and random effects, environmental index, inference space, prediction
Massively Parallel Nonparametrics in Neuroimaging

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Abstract. Given a sample of brain images, and associated clinical or demographic predictors, the standard modeling paradigm entails a collection of linear models, one at each of tens of thousands of brain locations (Friston et al., 1995). But in many applications, interest centers on \textit{nonlinear} dependence on predictors. For example, many studies have examined how image-derived quantities, such as functional connectivity or cortical thickness, vary with age at each point in the brain. The developmental trajectories are often not well described by linear or other parametric models, so that nonparametric regression with penalized splines is more suitable; but it has heretofore been impractical to perform spline smoothing in the massively parallel manner that these applications require. To surmount this difficulty, we introduce new algebraic techniques that make it feasible to compute huge numbers of optimally smoothed spline fits simultaneously. Our approach also enables testing a null hypothesis of linear dependence against a smooth alternative at each point in the brain, using a restricted likelihood ratio test (Crainiceanu and Ruppert, 2004). We adapt our methods to a completely different application: a refinement of higher-order diffusion tensor imaging for mapping the brain’s white matter architecture.

Keywords

higher-order diffusion tensor imaging, penalized splines, restricted likelihood ratio test, smoothness selection

References

Abstract. This talk will consider several motivating problems in translational neuroscience that lead to interesting statistical issues and is based upon the speaker’s long involvement with the Translational Neuroscience Program at the University of Pittsburgh. Focus will be on issues that have arisen from post-mortem brain tissue studies which are often employed for a number of psychiatric disorders to identify cellular biomarkers which distinguish subjects with the disorder from normal controls. The studies we consider use matched subject-control designs for sampling and tissue processing, with subjects chosen from a Brain Bank maintained at the University of Pittsburgh. The first motivating problem that we consider in this context is the efficient design of stereological tissue sampling schemes in order to test for population level differences. The other couple of issues we discuss arise from several projects with differing purposes, but which integrate results across multiple such studies with a goal to better understand the neurobiology of schizophrenia. One issue deals with using multiple studies to attempt to identify those neurobiological markers which best characterize schizophrenia and the other issue uses multiple studies to try to find clusters of subjects. There are specifics of the available data for both these projects that require new approaches in terms of structured multivariate models, mixture modeling, missing data, and discriminant techniques. The goal of our presentation is to provide a motivating overview of these issues and outline briefly some of our methodology.

(This is joint research with Josephine Asafu-Adjei (University of Pittsburgh) Qiang Wu (East Carolina University) and Wei Zhang (DVM, FDA).)
Generation Times in Epidemic Models

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Abstract. There has been recent interest in the so called generation time in epidemic models, i.e. the average time between the infection of a primary case and one of its secondary cases. It is related to the latent and infectious period distributions and is involved in a useful relationship between initial speed of growth and the basic reproductive number $R_0$ in SIR models. The natural framework for considerations about various times in epidemic models and analysis of their statistical properties is stochastic. Various facts about the generation time distribution will be presented and links to demography and statistics will also be discussed.

Keywords

generation time, epidemic model

References


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Abstract. Real time prediction of the final size and the turning point of the dengue outbreak are of primary interest from a public health point of view. Typically (i.e., Hsieh and Ma, 2009) a Richards model can be fitted to weekly dengue notification numbers in order to detect the turning point for the outbreak which enables us to study the impact of intervention measures relating to the turning point.

In this study we use fit several non-linear models for the outbreak data and use model averaging methodology to estimate both turning point and final size of the outbreak. The proposed methodology is applied to a single phase 2001 outbreak data from Havana city, Cuba.
A Measure of Explained Variation for Event History Data

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Abstract. There is no shortage of proposed measures of prognostic value of survival models in the statistical literature. They come under different names, including explained variation, correlation, explained randomness and information gain, but their goal is common: to define something analogous to the coefficient of determination $R^2$ in linear regression. None however have been uniformly accepted, none have been extended to general event history data, including recurrent events, and many cannot incorporate time-varying effects or covariates. We present here a measure specifically tailored for use with general dynamic event history regression models. The measure is applicable and interpretable in discrete or continuous time, with tied data or otherwise, with time-varying, time-fixed or dynamic covariates, with time-varying or time-constant effects, with single or multiple event times, with parametric or semi-parametric models, and under general independent censoring/observation. For single-event survival data with neither censoring nor time-dependency it reduces to the concordance index. We give expressions for its population value and the variance of the estimator and explore its use in simulations and applications. A web link to R software is provided.

Keywords

C-index, dynamic models, explained variation, rank correlation, recurrent events

References

Modeling Reductions in Breast Cancer Mortality

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Abstract. Reduction in breast cancer (BC) mortality in Western countries has been attributed to the use of screening mammography and to treatment improvement. We used a stochastic model based on previous works [1, 2] to quantify the contribution of each intervention. We estimated standardized BC mortality rates for the age group 30-69 per 100 000 women for calendar years 1975-2007 in four hypothetical scenarios: 1) Only screening, 2) Only treatment improvement, 3) Both, and 4) None.

Observed Catalan rates rose from 30.6 in 1977 to 37.5 in 1992, and afterwards continuously decreased to 23.1 in 2006. If none of the two interventions had been used, in 2006 the estimated BC mortality would be 43. Mortality reduction due to treatment improvement was higher than reduction due to screening. Taking as reference the scenario without any intervention, the mortality reduction in 2006 for only screening was 20% and for only treatment improvement 37%. With both interventions the reduction was 51%, this value is lower than the sum of the two individual contributions because there is a negative synergism between the two interventions (a difference of 6%).

The agreement between observed data and estimations from the model seem to indicate that the assumptions of the model and the inputs are correct.

Keywords
modelling, breast cancer, screening, mortality

References
Accounting for Prediction Error in Environmental Exposure when Relating Public Health to Environmental Factors

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Abstract. Publicly available data from disparate sources are increasingly combined for subsequent statistical analyses. Because data from different sources are frequently measured or associated with different geographic or spatial units, combining them for analysis usually requires prediction of one or more of the variables of interest. Here it is assumed that health outcomes and related covariates are measured at residences (points), that environmental exposure is measured at monitors (points), and that the two sets of points are mutually exclusive. To assess the association between the health outcome and environmental exposure, adjusting for covariates, the environmental exposure is predicted for the points for which health outcomes are observed.

When exposure is predicted using a smoothing method, such as kriging, Berkson error arises in the estimation of the parameter associated with environmental exposure in the regression of health outcomes on predicted environmental exposure, adjusting for covariates (Gryparis, et al. 2009, Szpiro, et al. 2011). As a consequence, the parameter is estimated unbiasedly (unlike with classical measurement error), but the standard error is biased downwards. Previously suggested methods for improving the estimated standard error will be briefly reviewed (Szpiro, et al. 2011; Lopiano, et al. 2011).

After aligning the health and environmental data sets using kriging, an iteratively reweighted generalized least squares approach is suggested for relating health outcomes and environmental exposure, adjusting for covariates. The properties of the method are discussed, and simulation results illustrate the performance of the proposed approach. Using the proposed methodology, the association between birth weight and air quality is explored, and the results contrasted to those obtained with other methods.

Keywords
sensitivity, specificity, marker, censored survival data

References


A Regularization/Extrapolation Corrected Score Method for Nonlinear Regression Models with Covariate Error

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Abstract. Many regression analyses involve explanatory variables that are measured with error, and failing to account for this error is well known to lead to biased estimates for the regression coefficients. We present here a new general method for adjusting for covariate error. Our method consists of an approximate version of the Stefanski-Nakamura corrected score approach, using the method of regularization for approximate solution of integral equations, along with an extrapolation device similar in spirit to that of the SIMEX method. Specifically, we compute estimates for various values of the regularization penalty parameter and extrapolate to a penalty parameter of zero. We develop the theory in the setting of classical likelihood models, covering nonlinear regression, logistic regression, and Poisson regression. The method is extremely general in terms of the types of measurement error models covered, and is a functional method in the sense of not requiring information on the distribution of the true covariate. We present a simulation study in the logistic regression setting, and provide an illustration on data from the Harvard Nurses’ Health Study concerning the relationship between physical activity and breast cancer death among patients with diagnosed breast cancer.

Keywords

errors in variables, nonlinear models, logistic regression
Contributed papers
Modelling the Mean and Covariance Structure for Continuous Bounded Longitudinal Data

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Abstract. In medical research it is common to measure patients' health status repeatedly over time through questionnaires. Based on the answers, summary measures such as scores can be derived. These scores will often have finite range, where one bound indicates 'no symptoms' and the other bound 'extreme symptoms'.

For a continuous and bounded score, the classical approach is to transform the data so that a linear regression model fits adequately. For some scores, however, a non-linear dependence of the transformed score on covariates persists. In addition, models based on transformations cannot investigate the dependence of bounds on covariates as the bounds need to be specified prior to the transformation.

In view of these limitations, we propose a non-linear mixed model for the mean score on the original scale as a function of covariates. The model is constructed for scores where the rate of recovery changes over time and has been motivated by the Collaborative Ankle Support Trial, which is a randomized controlled trial comparing four treatments for acute ankle sprains.

Apart from modelling the mean score, we discuss models for the covariance structure of bounded longitudinal data. With repeated measurements, we expect higher correlations when the measurements are closer in time than when they are further apart. Additionally, with bounded data, correlations increase as measurements reach the bound regardless of the time interval between measurements. Finally, the variances are rarely constant over time. A data-driven regression approach introduced by Pourahmadi [1999] is adopted and extended to allow for missing values.

Keywords

bounded data, non-linear mixed models, covariance models, missing data

References

Estimates of Clinically Useful Measures in Survival Analysis

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Abstract. In clinical studies where an event during patients follow-up is of interest, the analysis of the hazard ratio is generally used to measure treatment or covariate effects. In order to support clinical decisions, the estimate of different clinical useful measures should be directly considered, such as relative risks, excess of risks, relative risk reduction and number of patients needed to be treated.

The aim of this work is to provide a straightforward approach to obtain point and interval estimates of the above measures, by using transformation models, through suitable link functions. Modeling of the prognostic relationships in presence of variables measured on continuous scale and of putative time dependent effects is a challenge in this context. In order to use standard software for model estimates, the proposal of Klein and Andersen, based on pseudo-values, was considered as starting point. This approach, which was originally proposed to model competing risks and multi-state applications or as diagnostic tool for hazard regression, proved to be useful also in standard survival applications. The baseline risk function was estimated resorting to regression spline on time. Time-varying effects of covariates were tested through interaction with baseline time functions. A large literature data set on breast cancer was used for illustration.

Keywords
clinically useful measures, treatment effect, pseudo-values, time varying effects

References


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Penalized Likelihood Methodology and Applications

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Abstract. The penalized likelihood approach (Fan and Li, 2001), has been consistently demonstrated to be an attractive shrinkage and selection method. This procedure is different from traditional methods of variable selection in that it selects the significant variables and estimates regression coefficients simultaneously. As a result, the produced estimators are as efficient as the oracle estimator.

This new methodology was extended further to the case where we have survival data with censored observations and clusters, where the Cox proportional hazards model and the Gamma frailty model (Fan and Li, 2002) are the two commonly used semi-parametric models. This prompted us to extend the penalized Gamma frailty model approach and to propose a generalized form of the full likelihood function designed for clusters, which allows the direct use of many different distributions for the frailty parameter.

However, the performance of the penalized likelihood estimators depends on the proper choice of the regularization parameter. To this end, we firstly propose new estimates of the norm of the error in the generalized linear models framework, through the use of Kantorovich inequalities. Then these estimates are used in order to derive a tuning parameter selector in penalized generalized linear models.

Keywords
penalized likelihood, penalized frailty model, generalized linear models, tuning parameter estimation, error estimation

References

Performance of Markers for Censored Failure Time Outcome: Nonparametric Approach Based on Proportions

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Abstract. Nonparametric analysis of classification probabilities of markers used to detect the presence of disease at the time of marker measurement is based on inference on simple proportions. When disease status is subject to verification bias, weighting/imputation techniques enable to work again on proportions calculated on a classification matrix with available asymptotics. Inference becomes more complex because of censoring, when the marker aims at detecting the future development in time of disease. A fully nonparametric solution based on smoothed estimation of the bivariate survival function of time to disease and the marker was proposed, where bootstrap is recommended for asymptotics. Semiparametric approaches have also been developed. Here we consider censoring as a source of verification bias on the time to development of disease. Full and partial imputation of the disease status by Kaplan Meier estimation of survival functions conditional on the marker, and inverse probability of censoring weighting are used to obtain a censored corrected classification matrix. Classification probabilities are estimated by proportions which are proved to be equivalent to those obtained by the nonparametric approach. Our approach enables to derive asymptotic variance of sensibility and specificity and their covariance, using the delta method on logit transformations. The performance of the confidence interval for single sensibility and specificity, and the joint confidence interval for the two are investigated by simulations.

Keywords

sensitivity, specificity, marker, censored survival data

References


Forecasting Longitudinal Multivariate Binary Data

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Abstract. Longitudinal data involves repeated measurements taken from same subjects over time periods. The estimation power of longitudinal data models have been studied deeply. However, the forecasting feature of them have not been studied much. There are a few studies on forecasting with longitudinal data. Nonetheless, all of these studies are proposed for forecasting univariate response, and most of them are for continuous response. In this study, methods for forecasting longitudinal multivariate binary data are investigated. The multivariate forecasting results are compared with the univariate ones. A real life data set is used to illustrate the forecasting power of the models.

Keywords

multi-level models, generalized estimating equations, accuracy measures
Effects of Covariate Omission when Fitting the Fine-Gray Model to Data from Randomized Controlled Trials

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Abstract. In clinical trials, confounders are expected to be balanced between treatment groups, due to randomization. However, several studies have shown that omission of important predictors from models with non-linear link functions, lead to attenuated treatment effect estimates and loss of statistical power. In this work we explore the effects of omitting or categorizing an important covariate, when analysing data from clinical trials with competing endpoints, under the Fine-Gray model.

It can be shown that the omission or categorization of an important predictor in the Fine-Gray model leads, in general, in loss of proportionality. In order to explore various other aspects of the effects of covariate omission or categorization in the Fine-Gray model in clinical trial settings, we conducted a series of simulations. Different scenarios were defined according to the magnitude of the covariate’s effect on the event of interest as well as the variance of the covariate. 10 000 datasets were generated for each scenario. The number of subjects in each dataset was calculated based on the true treatment effect [subdistribution hazard ratio (SHR)=0.8], the expected proportion of failures from the event of interest and the desired power of 80%.

Simulation experiments showed substantial estimate attenuation of the treatment effect [Range of bias of log(SHR): 3.8% to 32.3%] and essential power loss (Range of power: 47.3% to 76.8%), when an important covariate was omitted from the model. Conditioning on a dichotomized version of a continuous covariate was associated with lower estimate attenuation and higher level of power (Range of bias: 1.4% to 17.1%; Range of power: 62.7% to 78.9%). Proper covariate adjustment resulted in unbiased estimates and power close to the desired level in all cases.

Since omitting or categorizing an important covariate leads to loss of proportionality in general, attenuated therapy effect estimates and significant power losses, we recommend proper adjustment for important predictors in the Fine-Gray model even in randomized controlled trials.

Keywords

Fine-Gray model, clinical trial, covariate omission
Modeling the Non-Inherited Maternal Antigens Effect in Multi-Case Families

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Abstract. Rheumatoid Arthritis (RA) is a complex genetic disorder. Alleles in the HLA-region form an important risk factor. One of these alleles, HLA-DERAA is known to have a protective effect. It is hypothesized that not only inherited but also non-inherited maternal antigens (NIMA) can increase resistance against RA. For case-parent designs several methods have been developed to model and/or test for the NIMA effect (Hsieh et al. 2006, Feitsma et al. 2007). However, these methods are not appropriate for families with multiple cases and healthy siblings. They ignore the information available for healthy siblings and the within-family correlation. In addition, they do not account for the outcome dependent sampling. To address the limitations of the current methods, we use family-specific random effect models and a likelihood based approach for estimation of NIMA effect parameters. In addition, to account for outcome dependent sampling schemes we will apply an ascertainment correction. We studied the performance of this method by simulations and found that large data sets and large families are required to estimate the NIMA effect. Therefore, we propose a meta-analysis approach that combines information from different studies to estimate the NIMA effect. To illustrate our proposed methodology we will use two studies, 82 case-parent and 205 control-mother families from The Netherlands and 89 multi-case nuclear families from the United Kingdom. In the Dutch case-parent trios the OR for DERAA-negative offspring of having a DERAA-positive mother compared to DERAA-positive father is 0.35 (95% C.I. 0.07-1.51). Finally, using the Ascertainment-Corrected Prospective Likelihood for the English families, the OR for the marginal NIMA effect was 0.17 (95% C.I. 0.01-2.08).

Keywords
ascertaintment, family-based association studies, mixed-effects models

References

Hierarchical Testing of Subsets of Hypotheses

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Abstract. As the size of large testing problems encountered in practice keeps increasing, more of these problems have further structure where the set of hypotheses can be partitioned into subsets of the hypotheses, and a discovery of some signal in a subset is of interest on top of the discovery of a signal in each of the many hypotheses on its own. Furthermore, the true state of the tested signals tends to be more similar within these subsets than across the subsets. Examples are regions in the brain in functional MRI research, sets of genes in genomic research, or geographical areas in disease outbreaks monitoring. The challenges in the analysis of such multiple testing problems will be discussed, and previous efforts to address them will be reviewed. We then present a few new methods to control various aspects of the False Discovery Rate, and discuss their benefits and limitations.

Keywords
false discovery rate, multiple comparisons, hierarchical testing, selective inference

References


Doubly Robust and Multiple Imputation Based Generalized Estimating Equations

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Abstract. Generalized estimating equations (GEE) is a popular method to analyze correlated non-Gaussian data. When data are incomplete, inferences under this method are valid only under the strong assumption that the missing data are missing completely at random. When response data are missing at random, two modifications of GEE can be considered, based on inverse-probability weighting or on multiple imputation (MI). The so-called doubly robust (DR) methods involve both a model for the weights and a predictive model for the missing observations given the observed ones. To yield consistent estimates, weighted GEE (WGEE) needs correct specification of the dropout model while imputation-based methodology need a correctly specified imputation model. DR methods need correct specification of either the weight or the predictive model, but not necessarily both. We study the relative performance of the singly and doubly robust versions of GEE in a variety of correctly and incorrectly specified models using simulation studies. Data from a clinical trial in onychomycosis further illustrate the methods.

Keywords
doubly robust GEE, multiple imputation, weighted GEE

References

The Influence of Rotation Type on the Repeatability of Dietary Patterns Derived through Principal Component Analysis

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Abstract. This study aimed to assess the role of rotation on the repeatability of dietary patterns derived through Principal Component Analysis (PCA). To test the research hypothesis 500 volunteers from the general population (37±15 years, 38% males) were asked to complete a valid 76-item Food Frequency Questionnaire (FFQ), twice within 20 days. The dietary patterns were a-posterior derived through PCA, with the application of the varimax and the promax type of orthogonal and non-orthogonal rotation respectively. Eight components (patterns) were derived from the application of PCA after the 1st recording of the FFQ and seven patterns were derived from the 2nd recording of the FFQ (eigenvalues >1). From the dietary patterns derived, four were considered nutritionally important, explained 38% and 40% of variance of dietary intake, respectively and were similar (repeatable) in both recordings. Four dietary patterns were also found repeatable when orthogonal rotation was applied, while when non-orthogonal rotation was applied three patterns seemed to be repeatable as derived from both recordings of the FFQ. In conclusion, when rotation is required to improve dietary patterns interpretation, non-orthogonal rotation seemed to provide more stable patterns, probably due to high intra-correlation between the extracted components.

Keywords
principal component analysis, rotation, repeatability

References
Analysis of Multirater Ordinal Data: An IRT Application

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Abstract. The analysis of ordinal categorical data when ratings from several judges are available is a framework which is still incomplete. There are many method of analysis proposed for this kind of data but all methods have their advantages and disadvantages. In this study we aim to evaluate the properties of Latent trait models in determining agreement among multi-raters. These properties will be discussed and compared with other methods proposed for multirater ordinal data. An application to a data set from dermatology will be given and compared with results obtained from other methods applied to the same data set.

Keywords

agreement, latent trait, ordinal, multirater, IRT
Adaptive Policies for Sequential Sampling under Incomplete Information and Side Constraints

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Abstract. Consider \( k \) independent populations. Successive outcomes from population \( a \) are i.i.d. random variables following distribution \( F_a(x|\theta_a) \), where \( \theta_a \) is an unknown parameter. Every time population \( a \) is sampled, a cost \( C_a \) is incurred.

We consider the problem of sequential sampling to maximize the expected infinite horizon average outcome per period, under a constraint that the expected sampling cost per period does not exceed an upper bound \( C_0 \).

If the vector \( \theta \) of unknown parameters were known, the problem could be formulated as a linear program with decision variables denoting the fraction of time that population \( a \) is sampled from, and \( z(\theta) \) the maximum outcome per period under complete information. In the incomplete information framework one is restricted to adaptive sampling policies, for which the selected population in any period can depend only on the history of decisions and sampling outcomes.

Let \( S_N(\pi, \theta) \) and \( J_N(\pi, \theta) \) denote the expected total outcome and expected total sampling cost, respectively, over horizon \( N \). A policy \( \pi \) is feasible if for all \( \theta \) it is true that \( \lim_{N \to \infty} J_N(\pi, \theta)/N \leq C_0 \). A feasible policy \( \pi \) is consistent if in addition its long-run expected average outcome converges to that under complete information for every value of the unknown vector: \( \lim_{N \to \infty} S_N(\pi, \theta)/N = z(\theta) \), for all \( \theta \). Thus, a consistent policy can identify the optimal sampling frequencies by experimentation only.

We show that a wide class of consistent policies exists, by a construction based on sampling blocks and sparse sequences of forced selections. To assess the efficiency of a consistent policy, we define the loss function \( R_N(\pi, \theta) = S_N(\pi, \theta) - N z(\theta) \) and consider the rate of convergence of \( R_N(\pi, \theta)/N \) to zero. We show that under the asymptotic form of the cost constraint, one can identify policies which violate the constraint for arbitrarily long time intervals, and still satisfy it in the long run, and thus artificially achieve expected average outcome above the complete information benchmark. This shows that the efficiency of a policy depends on the specific way that the constraint is enforced over finite intervals. To address this issue, we consider a stricter version of the cost constraint, under which the average cost per period must remain below \( C_0 \) for all finite horizons. We establish several properties of the loss function that pertain to the existence of efficient sampling policies.

Keywords

adaptive sampling, experimental design, clinical trials
Comparison of MB-MDR to BOOST and RAPID for Detecting Epistasis in Unrelateds

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Abstract. Recently, the Model-Based Multifactor Dimensionality Reduction (MB-MDR) method for epistasis detection was proposed [Calle et al. 2008]. It handles the dimensionality problem by pooling multi-locus genotypes into three risk groups. Model selection is based on association tests rather than prediction accuracy. Moreover, MB-MDR flexibly deals with different outcome types, allows adjustment for lower-order genetic effects and confounders, and is able to assess joint significance of multiple epistasis models. Empirical power and error rate of MB-MDR to detect epistasis were evaluated by [Cattaert et al. 2011]. In the present work, the performance of MB-MDR is compared to that of other state-of-the-art epistasis detection methods, including BOOlar Operation-based Screening and Testing (BOOST) [Wan et al. 2010] and RApid Pair Identification (RAPID) [Brinza et al. 2010]. For this purpose, we will use simulated data from [Wan et al. 2010] with 1000 markers. Disease status follows different penetrance models showing both main effects and epistasis.

Keywords

case-control data, epistasis, MB-MDR, BOOST

References


Modelling Occupancy-Abundance Patterns in Supra-Specific Taxa of Soil Invertebrates from Zambia and India

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Abstract. Although positive inter-specific and intra-specific occupancy-abundance (OA) patterns have been widely reported, information is virtually lacking on OA patterns at taxonomic resolutions coarser than the species. We model OA patterns in soil invertebrate assemblages from eastern Zambia and South-western India with the objective of testing the following hypotheses: (1) OA relationships do not exist at supra-specific taxonomic levels, and (2) if such relationships exist, the OA curve will be different for assemblages from isolated regions. We tested these hypotheses by fitting various empirical and theoretical models to the datasets of various taxa. The analyses provided new evidence for a positive relationship between abundance and occupancy in the context of supra-specific taxa. The analyses also demonstrated a striking effect of zero-inflation and spatial aggregation on the shape of the OA curve. The zero-inflated Poisson (ZIP) and zero-inflated negative binomial (ZINB) models predicted that abundance can increase without commensurate increases in site occupancy when the zero-inflation probability is large.

Keywords

occupancy-abundance, taxonomic sufficiency, zero-inflated negative binomial, zero-inflated Poisson

References

Herd-Prevalence based on Aggregate Testing of Animals

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Abstract. It is common practice that some or all animals in a group of animals, e.g. a herd, are tested for their health status by using a diagnostic test to investigate whether the herd is infected by a disease. Several obstacles complicate the estimation of herd prevalence on the basis of test results of the animals. First, diagnostic tests are often imperfect, resulting in a misclassification of the animal’s disease status. It is well known how to correct the animal’s apparent prevalence by using the diagnostic sensitivity and specificity of the animal test, but the effects on herd prevalence are less clear. Sometimes, the sensitivity and specificity of the test are used to correct the herd prevalence directly by using a Rogan-Gladen estimator. It is shown that the test characteristics of a single test are not the same as for a group of tests, and this ad hoc procedure would lead to biased results. Second, in practice, a herd is often defined as positive when at least one sampled animal tested positively. This definition is ambiguous and is also different from the herd prevalence that is based on having at least one diseased animal in the herd. In this presentation, a discussion of these aspects is given and a method is proposed to estimate the true herd prevalence on the basis of the health status of (all or a sample of) animals within a herd corrected for the sensitivity and specificity of the individual test, the number of animals that are tested in the herd and the uncertainty of the diagnostic test characteristics. The beta-binomial model lies at the basis of the proposal, and allows to correct for (a) the within-group correlation, (b) the diagnostic characteristics of the used test and (c) the sampling design. The methodology will be exemplified on a survey of Bluetongue in cattle herds.

Keywords
animal prevalence, beta-binomial model, diagnostic tests, herd prevalence

References
Abstract. Count time series are observed in diverse applications, for instance consider the number of transaction per minute of some stock, or the monthly number of people with a certain disease, and so on. For the analysis of these data, there has been developed a number of models based either on thinning operator or on GLM framework. We will be examining the second class of models which include a feedback mechanism. Such models are expected, in general, to be more parsimonious, pretty much as is the case of GARCH models. It is important therefore to study their statistical properties and develop algorithms for estimation and prediction. In this contribution we discuss the problem of estimation of mixed Poisson autoregressive model with an emphasis to a biostatistical application.

Keywords

autoregression, count data, mixture distributions
Trends in Mammographic Breast Density and Risk of Breast Cancer

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Abstract. To improve screening, the identification of markers that discriminate between minimal-risk and high-risk disease has been recommended. Also, women and physicians are increasingly encouraged to use risk models to make decisions about prevention and early detection of breast cancer. There is evidence that breast density and its changes over time are related to breast cancer risk. The objective of this study is to assess the association of baseline breast density, and its changes over time, with breast cancer incidence. A further goal will be to incorporate the findings of this study into some of the existing risk assessment models.

Data was from 13,757 women participating in the Breast Cancer Screening Program (BCSP) in Sabadell-Cerdanyola, Catalonia, Spain, from October 1995 to July 2010. The BCSP targets women aged 50 to 69 years and the exams are performed biennially. There were 458 women from the sample that developed breast cancer. Breast density was measured using the BI-RADS system, collected prospectively at every screening exam. Mixed-effects cumulative logit models have been used to assess trends over time and their interaction with the diagnosis of cancer. Preliminary results show 1) a reduction of breast cancer density over time, and 2) increased breast cancer risk in women that have higher density at baseline.

Keywords
breast cancer, breast density, longitudinal data, cumulative logit models

References

The Presence of the Absence in a Geriatric Cohort: Functional Decline Curve Accounting for Attrition

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Abstract. Decline in walking speed in the elderly was shown to be the most persistent predictor for mobility limitation and mortality in several cohort studies of older people (1). However, the mean decline is not fully captured by the observed means due to the attrition structure and under-representation of dropouts. This leads to increasing bias in the estimation of the decline curve when a naive method is used. Most methods which are covered in a recent monograph on missing values regard the absence of a values as an aberrant and the values may be recovered by suitable methods (2). In contrast, in geriatric cohort studies incomplete data due to attrition is an expected natural process and requires an adaptation to the methods presented in the monograph. The objective of this work is to evaluate walking speed decline curve in a geriatric cohort accounting for bias due to attrition and death. The Health, Aging, and Body Composition (Health ABC) study is a cohort study conducted by the National Institute on Aging (NIA). Eligible cases were recruited in Pittsburgh and Tennessee during 1997-1998 and are followed to date. The analysis included data for all subjects having year-1 or year-2 20 meter usual walking speed (U20MSD), \( n = 2,999 \). At year-10 only \( n = 1,426 \) had valid observations; there are a total 17,560 available observations, increasing to 18,689 monotone observations by imputation of intermittent missing data. We have studied the dropout and death pattern by computing the probability of being observed at year \( t \), \( R_t \) given the value \( Y_{i,t-1} \) and slope (SLOPE\(_{i,t-1} \) leading to previous year using GEE with logit link: \( P_{it} = P(R_{it} = 1/Y_{i,t-1}, SLOPE_{i,t-1}) \) for year > 2, \( P_{it} = P(R_{it} = 1/Y_{i,t-1}, 1) \) for year = 2 and \( P_{it} = P(R_{it} = 1) \) for year = 1. We further obtain weights \( W_{it} \) based on the inverse: \( W_{it} = 1/P_{it} \). These weights were applied to the computation of the means of the decline curve. Results: The weighted means showed a larger decrease over time in comparison to the decrease seen in the available data means. The weighted means had a decrease of 24% over 10 years. Conclusions: We demonstrated that controlling for attrition in the estimation of the decline rate has resulted in estimation of a larger decline over time. This trend was expected yet it supports our future efforts in developing methods suitable for geriatric cohort. We plan to further explore W-GEE method to model the decline process in the presence of cofactors along with the attrition process of various subsets.

Keywords
incomplete data, inverse probability weighting, GEE

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A Classification of the Main Biometrical Methodologies Applied in Agricultural Experimentation and Research

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Abstract. Scientists who study biological phenomena quickly realize that a main part in their work has the variation appearing in living organisms. It is exactly the variation in the environment and in the response of living organisms to each other and their environment that provides scientists with both a challenge and a prospect. Definitely, Fisher's work (1925) in conjunction with the vast increases in computer power that were implemented after the 1960s, have made possible much more efficient and exciting methods of data analysis, thus opening the "bag of Aeolus" for the application of modern statistical techniques in agricultural experimentation and research.

Nowadays, the development of new statistical software has allowed scientists to make the best use of experimental resources to meet stated objectives, that is, to design better experiments and surveys, as well as to analyze them more efficiently. As a part of these, agricultural scientists are able to explain the variation in their experiments, applying the most refined biometrical methodologies and combining them with the results of relative works in their field.

This study mainly seeks to classify biometrical methodologies that have been used in the agricultural research, emphasizing in the segregation of the agriculture in seven separate scientific fields, in order to be used as the most appropriate guide for the scientists of each specific agricultural field in choosing the most suitable methodology in their research.
Measuring Follow-up Completeness in Survival Studies

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Abstract. In studies with a survival endpoint, censoring can occur because of drop-out or because the study ends before the event has happened. Censored observations can be included in the analysis in both cases. While censoring by the end of study introduces no risk of bias, drop-out clearly does. Therefore, study reports should include information on the completeness of follow-up, especially in clinical trials.

We propose a simple measure $C_F$ that expresses completeness as the percent ratio of total actual over total potential follow-up times. The numerator is derived from the Kaplan-Meier estimator of the censoring distribution, obtained by reversing 'censor' and 'failure'. The denominator is the total of potential follow-up times, i.e. the sum over individual times from study entry to the end of study.

Clark, Altman and De Stavola [1] introduced a similar measure of completeness of follow-up $C$, and a modified version $C^*$ was proposed by Wu, Takkenberg and Grunkemeier [2]. Our measure $C_F$ amends the previous ones, because it reflects the drop-out mechanism but is unaffected by the survival distribution. $C$ has been criticized for lacking this crucial property [3], especially in clinical trials where survival can depend on treatment. We demonstrate the performance of $C$, $C^*$ and $C_F$ in a simulation study and a clinical trial in breast cancer.

Keywords

clinical trials, completeness of follow-up, drop-out

References

Statistical Methods for Evaluating Prognostic Features of Single Nucleotide Polymorphisms (SNPs) in Critical Signal Pathways for Renal Cell Carcinoma (RCC)

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Abstract. With the increased availability of genomic data and the pursuit of personalized medicine, there is growing interest in using genomic information to augment clinical prognostic factors to predict disease outcomes. The analysis of genomic data, however, often involves challenging issues such as highly-dimensional data, multiple comparisons, and biological heterogeneity or population stratification. In this talk, I will discuss some of our experiences and thoughts on the methods and criteria used in selecting SNPs that potentially implicate the significant prognostic features on the outcomes of interest. We use a renal cell carcinoma project as an example. Methods for multiple comparison adjustment, false discovery rate (FDR), permutation based tests, and non-permutation approaches for controlling average FDR as well as the interpretation of such analysis results will be discussed.

Keywords

genomic association, multiple comparison, FDR, permutation tests

References


Longitudinal CART and its Application in Neuroimaging Studies

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Abstract. Study of many medical conditions is challenging because of their heterogenous nature. For example, neurocognitive impairment (NCI) observed in HIV-infected patients is hypothesized to be caused by a combination of the host, clinical, imaging and treatment factors. To allow a discovery of the most predictive marker combinations, we use Classification and Regression Trees (CART), Breiman et al. (1984) in a cross-sectional setting. To study the development of NCI, we apply and extend a recently proposed, RE-EM Trees, method (Sela and Simonoff, 2009), which takes into account the correlations between the observations on the subjects in the construction of a regression tree. However, the RE-EM Tree method is not suitable for a study of an influence of baseline covariates on the longitudinal trajectories. Our approach combines the linear mixed models and the regression trees and is geared specifically towards finding combinations of baseline factors influencing the rate of change in a outcome variable. We apply our method to the study of changes in the volumetric (MRI) and metabolic (MRS) patterns as well as development of NCI in a group of HIV-infected patients.

Keywords

magnetic resonance spectroscopy, magnetic resonance imaging, classification and regression trees, linear mixed models

References

Marginalized Models for Bivariate Longitudinal Binary Data

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Abstract. In this paper, we propose a multi-level model for bivariate longitudinal binary data related to the one proposed in Fitzmaurice and Laird (1993). For the first level, a logistic regression is used to model the marginal mean of the longitudinal response. On the second level, the joint distribution of the bivariate responses at a given time is specified. The third level introduces a Markov transition structure to account for serial correlation within a multinomial logistic regression model. Different from Fitzmaurice and Laird (1993), this specification is more natural to exploit the type of correlation typically seen in longitudinal data. Markov Chain Monte Carlo Methods, specifically Gibbs sampling with guided walk steps, are used to sample from the posterior distribution of parameters. The proposed computational algorithm is expected to be faster than the iterative proportional fitting procedure, which was adopted in Fitzmaurice and Laird (1993), especially for moderate and large series. The methods are illustrated on a real life dataset.

Keywords

Bayesian hierarchical model, within-subject dependence

References

An Improved Cusum Procedure for Detection of Outbreaks in Poisson Distributed Health Events

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Abstract. A new cusum method for detecting outbreaks in health events is proposed. It is based on a standardized statistic with a bias from zero that can be neglected. Alarming boundaries are determined from the actual distribution of the statistic rather than from normality assumptions. The boundaries are furthermore determined from requirements on the probability of false alarms, instead of the common practice to focus on average run lengths (ARLs). The new method is compared with other cusum methods (Rossi et al, 1999) in Monte Carlo simulations. The new method turns out to have the same sensitivity and the same expected time to first motivated alarm. However, the new method has expected times to first false alarm that are 9% - 90% longer. The performance of the various methods is demonstrated on data consisting of outbreaks of sick-listening and of outbreaks of Chlamydia infection. The paper also contains guidelines for choosing proper length of sampling periods and of reference value (k).

Keywords

reference value, sampling and calibration periods

References

Bayesian Semiparametric Modeling for Nonignorably Missing Covariates

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Abstract. In missing data problems, the missing data mechanism is modeled taking a fully parametric approach which rules out the possibility of a nonlinear relationship in the missing data mechanism. Chen and Ibrahim (2006) considered a class of semiparametric models for missing data mechanism. We too consider semiparametric models for the missingness mechanism of nonignorably missing covariates. In our model the relationship between the missingness probability ($p_i$) and the missing covariate is modeled through splines. This way, the possibility of nonlinear relationship between the actual value of the missing covariate and the $p_i$ is accommodated. A WinBUGS code is constructed to conduct the posterior calculations for Bayesian estimation. A Monte Carlo simulation experiment is carried out to investigate the bias and efficiency properties of our estimators compared to the estimators from the fully parametric approach. Our work differs from Chen and Ibrahim (2006) in two major aspects: they i) modeled, in their simulation study, the fully observed covariate semiparametrically, ii) used MLE. We model the missing covariate semiparametrically motivated by the fact that there is not sufficient information in the data set about the true nature of the relationship between the $p_i$ and the missing covariate. With the same motivation, we use Bayesian paradigm to gather information via priors constructed with Empirical Bayesian method (in addition to the information provided by the likelihood). Our results show that the proposed approach has better bias and MSE properties than the parametric approaches.

Keywords

generalized additive model, Gibbs sampling, WinBUGS

References

Importance of Hazard Functions for Lifetime Data

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Abstract. Data belonging to lifetime contain nonnegative measurements and the distribution appears positively skewed. The most crucial characteristic of lifetime distributions in order to decide which distribution is appropriate for the data is their hazard functions. In this study, principal lifetime distributions such as Exponential, Gamma, Weibull, Lognormal and Inverse Gaussian (IG) distributions were considered in terms of their hazard functions. In medical studies, distributions which has non-monotonic hazard function can be appropriate, because when a person catches a fatal disease hazard function of his/her lifetime will not be monotone any longer. In this case, Lognormal and IG can be thought as the appropriate distributions, because their hazard functions demonstrate a high occurrence of failure at the beginning of the disease. When time goes to infinity, hazard function of IG tends to go to a certain value different from zero but the Lognormal tends to go to 0. Hazard function belonging to lifetime data of human beings can never take a value like "zero", because human beings are mortal. Our aim is to present how IG distribution fits well to lifetime data of human beings in respect to hazard function.

Keywords
inverse Gaussian, hazard function, lifetime of human beings

References


Quality Adjusted Survival Analysis of Postmenopausal Breast Cancer

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Abstract. Quality of life in some diseases such as cancer or chronic diseases, may influence the success of medical and psychosocial treatment. The reason of this is that given drugs or treatments (such as chemotherapy or radiotherapy) have negative effects on the quality of life. In these types of diseases; in order to show a new treatment is more effective than the old one, it should not affect the quality of life beside to extend the duration of survival time. Thus; the survival time of a patient has to be assessed in terms of quantity and quality. Therefore, statistical methods are required to evaluate the both survival time and quality of life.

One of these statistical methods is Quality Adjusted Time Without Symptoms of Disease or toxicities of Treatment (Q-TWiST). Q-TWiST is used when comparing the effectiveness of different treatment methods, technics or drugs. Q-TWiST makes comparisons in terms of quality and length of life simultaneously by considering treatments which has negative effects on quality of life, prolongs the survival time or increases the quality of life. This method is based on the estimate the adjusted survival time by correcting the effect of quality of life on certain follow-up periods. Weights indicating the quality of life of periods vary between 0 and 1. The value of 0 represents the poor quality of life (death) and the value of 1 shows the excellent state of health. These weights are called as utility coefficients. Survival times in groups of different treatments or drugs, are compared according to these adjusted times.

Threshold Utility Analysis is performed to show that different treatments give different results on different combinations of utility coefficients.

In this study, Q-TWiST analysis will be applied to postmenopausal breast cancer data.

Keywords

quality of life, survival analysis, postmenopausal breast cancer
A Graphical Approach for Adaptive Clinical Trials
Testing Multiple Hypotheses

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Abstract. Recently a graphical approach to define multiple testing procedures based on weighted sequentially rejective tests has been proposed [1]. This provides a visually accessible tool for the construction of procedures, that reflect the complex contextual relations between multiple hypotheses in clinical trials. We extend this approach to adaptive designs with an unblinded interim analysis. Such designs are a popular choice for confirmatory clinical trials as they provide type I error control while permitting certain mid-trial design modifications based on internal and external information, e.g., changing the pre-planned sample size, inserting/dropping of treatment groups and endpoints in clinical trials. Our approach is based on the closed testing principle combined with the conditional error principle. Starting with a closed testing procedure based on weighted Bonferroni tests we construct, for all intersection hypotheses, a second stage test at levels equal or smaller than the sum of marginal conditional error levels of the initial tests [2,3]. Using marginal conditional errors, knowledge of the multivariate distribution of the test statistics is not required making our approach suitable for, e.g., comparing treatment groups and/or multiple endpoints.

Keywords
multiple testing, adaptive designs, biostatistics

References

Assessing Non-Inferiority in a Gold Standard Design for Retention of Effect Hypotheses - A Semiparametric Approach

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Abstract. We develop a statistical methodology for planning and evaluating non-inferiority trials. In particular, a gold standard design (consisting of an experimental treatment, an active reference and a placebo) is considered and the data are assumed to be right censored. The efficacy of the treatments is measured via hazard functions that are modeled by the Cox-Proportional-Hazards model. We develop a new semiparametric non-inferiority test procedure, only assuming proportional hazard functions. Moreover, we present an algorithm for calculating the sample size and its best allocation to assure that a prespecified power is attained. Finally, we compare our procedure with a known existing parametric one which is based on exponential distributed data. We show that the resulting sample size of both procedures do not differ too much. However, the parametric procedure has got an important drawback as it is not robust against a violation of the distribution assumption, whereas our method does not fail.

Keywords

non-inferiority, gold standard design, censored data, semiparametric, retention of effect, sample allocation
Robust Estimation in Cox Proportional Hazards Model

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**Abstract.** When the study of interest in survival analysis is the effect of covariates, a regression model is useful. Proportional hazards (PH) model proposed by Cox (1972) has been widely used for modeling the relationship between the survival time and a set of covariates. Cox PH model specifies the hazard rate of failure for the survival time $T$ of an individual given the covariate vector $Z$. A key property of this model is that, for different values of $Z$ the hazards functions are proportional to each other such that their ratio is independent of time $t$. The parameters in Cox PH model are estimated through partial likelihood (PL). However, the partial likelihood is sensitive to violations of the model assumptions, including varying dependency structure of survival time and covariates, measurement error in covariates and identification of influential observations. Using the partial likelihood method for estimating parameters in the Cox PH model can produce biased results. To cope with this problem, robust estimators can be used. In this study, as an alternative to partial likelihood method (PL), robust estimation method (RE) proposed by Bednarski (1993) and Minder and Bednarski (1996), has been used to estimate parameters. A simulation study has been done and, the results of PL and RE have been compared.

**Keywords**

Cox regression, partial likelihood, influence points, robust estimation

**References**


Variable Selection and Computation of the Prior Probability of a Model

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Abstract. The behavior of Receiver Operating Characteristic (ROC) curves is examined by comparing multiple tests, i.e., different types of predictor variables with a binary outcome (y=1 or y=0). ROC analysis is compared to a standard method in classification problems, the Logistic Regression, and is discussed as an alternative method to identify the significant predictor variables.

The prior probabilities of the respective populations play a key role. However, those probabilities are largely ignored in the construction of high-dimensional models. Nevertheless, including information about prior probabilities can reduce the overall error rate (Hall and Xiao, 2010).

We firstly propose a variable selection approach to reduce error rate in this way and compute simultaneously the prior probability of a statistical model. The proposed method is simple and explicit to apply, and does not involve choice of any tuning parameters. Also, the empirical study reveals a new modification ($\text{mBIC}_R$) of the already modified Bayesian Information Criterion (mBIC) (Bogdan et al. 2008). Then extensive simulations are performed with satisfactory results and the proposed method is applied for variable ranking on high-dimensional real medical data.

Keywords
multiple testing, variable selection, maximum likelihood estimation, logistic regression, ROC, prior distribution, modified BIC, trauma

References

Cross-Validation Prior Choice in Bayesian Probit Regression with Many Covariates

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Abstract. In gene expression data we are quite often interested in finding few genes among several hundred of them that discriminate between two disease states. This has lead to interest in the use of variable selection methods for binary regression models with many regressors. In this work, we adopt the Bayesian variable selection method for probit regression with a Gaussian ridge-type prior on the regression coefficients and take full consideration of the variable inclusion uncertainty by Bayesian model averaging. The shrinkage parameter of the ridge prior is elicited by an empirical Bayes approach that chooses as shrinkage parameter the minimizer of a K-fold cross-validated log predictive score. Cross-validation is particularly useful in this context because it avoids the tendency of such models to fit perfectly. The log predictive score does not have a closed analytic expression and needs to be estimated by sampling methods. Naive MCMC evaluations of the log predictive score require substantial computational effort and we investigate computationally cheaper methods using importance sampling. In comparison to MCMC methodology, importance sampling makes repeated use of the same simulated sample to estimate the log predictive score at any value of the shrinkage parameter. The first proposed importance sampler is mixing over different values of the shrinkage parameter and the second one is integrating over the shrinkage parameter through an auxiliary distribution. These methods are applied to gene expression data and result in almost ten-fold computational improvement over the MCMC approach.

Keywords

Bayesian variable selection, ridge prior, cross-validation, predictive score, importance sampling

References

A Longitudinal Study of the Effect of Physical Activity on Risk of Heart Failures: Methods and Applications

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Abstract. Physical activity is known to decrease mortality and increase quality of life in persons with manifest heart failure, but whether habitual physical activity can lower the risk of heart failure needs to be better investigated. In a cohort of 43880 Swedish men and women, followed for 9 years, intensity and frequency of physical activity were studied. Given the complexity of the possible pathways linking physical activity and heart failure, possible causal diagrams were identified and possible strategies of analysis proposed. Standard regression models for analyzing time to event data were fitted, hazard ratios and confidence intervals were produced. Maximum likelihood based tests were used to assess the significance of the main and interaction variables. Multiple imputation methods based on chained equations sampling were used to increase the efficiency of the estimates, and flexible regression models were fitted to study non linearity. Initial results show that, after adjusting for possible confounders, a low level of physical activity still present higher risk of heart failure.

Keywords
physical activity, congestive heart failure, survival analysis, epidemiological methods
Handling Missing Data: A Strategy Based on Multiple Imputation and Bayesian Analysis

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Abstract. In clinical research, whatever the application, handling with missing data is a real and major challenge. Classification of missing data based on the withdrawal information is very well known and strategy of replacement are described in scientific and regulatory literature. Another important difference is the nature of the parameter (primary or secondary) and the replacement strategy will also depend on the "interest" of this variable. In the meantime, bayesian methods have been developed and start to be recognised by regulatory as valid and of interest.

In this presentation, we describe the current state-of-art in handling missing data and also some considerations to use bayesian methods to deal with replacement. Comparisons between the two approaches based on simulations and interpretation limits will also be presented. A special focus will be made on the EM- and MCMC-methods.

Such strategy has been applied on a clinical study in nutrition to handle missing data. We will discuss statistical as well as interpretation strengths and limits of two strategies.

Keywords
missing data, multiple imputation, Bayesian, MCAR, MAR
Meta Analysis for Summarizing Results of Simulation Studies: One-Way ANOVA and its Some Alternatives Cases

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Abstract. There are many simulation studies, which ANOVA-F test is compared to its some parametric and non-parametric alternatives in terms of type I error rate (α) and power of the test (1 − β) in cases where two important assumptions of analysis of variance; normality and homogeneity are not met. However, the results of these studies indicate that the values of probability of type-I obtained and of the power of the test show large variation due to differences of the study conditions (distribution shape, variance ratios, sample size, relations between sample size and variance ratios, number of simulation, number of group, etc.). Large differences among the similar studies limit the researchers benefit from these studies. In such cases, gathering of the findings of these studies in a suitable way and their analysis is regarded as an efficient solution. Meta analysis was used to summarize the results of Monte Carlo simulation studies of the robustness of the one-way fixed effect ANOVA-F test and its some alternatives such as Welch test, Brown-Forsythe test, James second-order test and Kruskal-Wallis test. The results indicate that there is a statistically significant relationship between type I error rate and variance ratio, relationships between sample size and variance ratio (direct and inverse pairing), number of observation in each group, and distribution shape for all tests. The same relations are also valid for test power. The effect of simulation number on type I error rate test power is obvious when the number of simulation is less than 10000. However, when the simulation number is greater than 10,000, this effect decreases at a negligible level. The type I error rate and test power of the F test were very sensitive to unequal variances, even when sample sizes were equal. The type I error rate and test power of the Kruskal-Wallis test were also sensitive to unequal variances. The type I error rate and test power of the Welch test and Brown-Forsythe test were insensitive to unequal variances when the population distribution was normal and number of observations in each group was ≥ 10, but the deviations from normality tended to inflate their type I error rates and to decrease their power.

Keywords

meta analysis, simulation, analysis of variance, type I error rate, test power
Calibration Comparison of Instruments for Measuring Particle-Mass Concentrations, in the Presence of Random Effects

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\textbf{Abstract.} We consider a problem of comparing different instruments for measuring particle-mass concentrations. For each instrument we have a calibration set \{\((x_i, y_i)\}\), comprising the instrument’s inexact measurements \(y\) together with precise measurements \(x\) (obtained by a different method). We wish to choose the instrument such that for a future measurement \(y_0\) corresponding to an unobserved \(x_0\), the estimated (predicted) \(x_0\) will be as accurate as possible.

For one instrument with linearly related \(x_i\) and \(y_i\), this is a standard problem in calibration. Estimating the regression coefficients \(\beta_0\) and \(\beta_1\) and “inverting” gives the classical estimator \(\hat{x}_0 = (y_0 - \hat{\beta}_0)/\hat{\beta}_1\), and confidence intervals can be obtained using a fiducial approach (Fieller, 1954). For several instruments, if each instrument was used to measure the same exact (but unobserved) \(x\)-value, they can be compared using errors-in-variables techniques. This is known as the comparative calibration problem, and extensive results are available (Osborne, 1991).

Our problem, however, is more complex for two reasons. First, the calibration set for each instrument comprises several sets of measurements (obtained at different locations and at different times), and the regression of \(y\) on \(x\) varies with this. Thus, the data need to be analyzed using a mixed model, and the random effects need to be taken into account at the prediction step. Second, the calibration sets have different \(x\) values for each instrument. Since the accuracy at the prediction step depends, among other factors, on the location of \(x_0\) relative to the \(x\) values in the calibration sample, comparing the instruments is more complicated.

Calibration point estimates and confidence intervals have already been developed in the context of random effects (Oman, 1998). In this talk we shall discuss methods of quantifying the accuracy of these estimates and intervals in such a way that we can easily compare instruments using data from different calibration sets.

\textbf{Keywords}

calibration, comparison, mixed model

\textbf{References}


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A Simulation Study Based on Nonlinear Mixed Effects Models

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Abstract. In this study, we compared four different clinical protocol designs to analyze HIV dynamics. It was investigated that whether earlier samplings can result in more useful information about the viral load trajectory, especially with respect to the decay rate in phase one. Furthermore, the best scheme is selected based on efficiency criteria and simulation study has been repeated to investigate the effect of increasing number of subjects on parameter estimations. There are many clinical studies of HIV dynamics currently run in the world. Many of the HIV dynamics models are developed to measure short-term dynamics. While these models reflect well the short-term viral dynamics, they do not describe the long-term viral dynamics adequately. Thus, different models are needed to estimate viral load parameters at the earlier and later stages. In this study, a semi-parametric nonlinear mixed effects (SNLME) model is used for modelling long-term HIV dynamics. Lindstrom-Bates algorithm is employed for fitting SNLME model and a simulation-based approach has been applied to compute mean square errors (MSE) for four different protocol designs. MSE values are found to be 0.00233, 0.00203, 0.00289 and 0.00258 for first, second, third and fourth clinical protocol designs respectively. The second design which has the least MSE value has been chosen as a best design scheme. Also, according to simulation study which has been repeated it is found that MSE value is decreasing when the number of subjects increasing, however, after a certain point this decrease is stabilized.

Keywords
nonlinear mixed effects models, HIV dynamics, clinical trial simulation, protocol designs, Lindstrom-Bates algorithm

References
Utilizing the Clinical DataFax System from Randomization to the Completion of a Clinical Trial

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Abstract. The successful clinical trial require a system that can collect and manage the data with quality, flexibility, and traceability. In order to have the most reliable clinical trial data, the early communications should be conducted among the relevant people, such as the study coordinator, statistician, data manager and programmer. The meetings are used to gather requirements and specifications for the study, and to determine the data collection and management system for the clinical trials. The data collection for the clinical trials may be done by various methods such as paper, fax or electronic based and the management of this data requires extensive human interactions and resources. The previous paper-based clinical trial study managed by the Frontier Science and Technology Research Foundation (FSTRF) was very labor intensive with much room for human error due to the multiple transcriptions of the data. The Clinical DataFax System was selected as the data management software in a randomized, controlled clinical trial conducted at a single institution with several clinic offices.

The DataFax system was chosen on the basis of the data acquisition and management capabilities to conduct clinical trial with a budget and flexibility to adjust possible changes in the protocol. The DataFax system allows implementation of case report forms (CRFs) in a fairly reasonable time and is flexible enough to allow for the simplest to the most complicated data management situations. The edit checks, CRF collection process and data schema are constructed according to the protocol. The specifications also allowed us to test and validate the DataFax study setup process before the data collection process began.

The DataFax system was utilized successfully to automatically randomize and number eligible subjects. The information was then e-mailed to the coordinating office. The quality control report was extensively used to obtain clean data. The data export process for the analysis has been seamless.

Keywords

clinical trials data
Nonparametric Regression of Mean and Covariance Structures for Longitudinal Data

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Abstract. When analyzing longitudinal/correlated data, misspecification of covariance structures may lead to inefficient estimators of parameters in the mean. In some circumstances, e.g., when missing data are present, it may result in very biased estimators of the mean parameters. Hence, correct models for covariance structures play a very important role in statistical modelling. Like the mean, covariance structures can be modelled using parametric or nonparametric regression model techniques. Various estimation methods were developed recently to model the mean and covariance structures, simultaneously. In this talk, I will start with a brief review of literature work on covariance modelling and then focus on joint modelling of the mean and covariance structures for longitudinal data using nonparametric regression techniques. Estimation methods will be developed and theoretical properties will be given. Real examples analysis and simulation studies will be provided and comparisons to the literature work will be made.

Keywords
covariance models, longitudinal data, modified Cholesky decomposition, nonparametric regression

References

Censoring Biomarker Measurements due to Treatment Initiation: Ignorable or Not?

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Abstract. HIV virus infects vital cells (mainly CD4) of the immune system and, if untreated, leads to AIDS. Combination antiretroviral therapy (cART) acts by suppressing viral load and increasing CD4 levels in most cases. The CD4 rate of decline prior to cART/AIDS is of great interest but censoring CD4 measurements taken after these events may affect the validity of various analyses. Censoring due to AIDS or death is most probably non-ignorable since the probability of these events is likely to be associated with unobserved quantities such as the latent CD4 trends. On the other hand, initiation of cART is based mainly on observed CD4 measurements thus the corresponding censoring mechanism should be ignorable. In this study we are using simulations to evaluate the performance of mixed models in terms of bias and precision when series of CD4 measurements are censored at cART initiation.

We generated 1000 datasets of CD4 measurements (4/year for 20 years) on 1000 subjects according to a random intercept/slope model and 1000 more with correlated CD4 and viral load measurements according to a similar bivariate model. cART initiation was based solely on CD4 or CD4 and viral load, as most current guidelines suggest, thresholds. Models' parameters were based on real data analyses.

Mixed models yielded practically unbiased estimates of the CD4 slope (relative bias: 1.32% to 1.70%). When cART initiation was based on CD4 and viral load thresholds, univariate analysis of CD4 data yielded a 9.53% bias for the estimate of CD4 slope but a bivariate analysis of CD4 and viral load data yielded unbiased results (-1.17% bias). Finally, when we assumed different CD4 thresholds for cART initiation for two otherwise equivalent groups, all estimates were still practically unbiased and the rate of false positive findings, regarding between groups differences, was below 2%. In most scenarios standard errors were slightly underestimated, leading to 95% coverage probabilities which ranged from 0.867 to 0.956.

In conclusion, mixed models seem adequate for analyzing censored series of longitudinal data provided that the censoring mechanism depends on observed data and all of them are included in the analysis.

Keywords

longitudinal, missing, censoring, HIV, HAART
Optimal Variable Selection for Regression Models

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Abstract. When building regression models based on datasets with a large number of predictive variables, there is the need for methods to conduct an efficient selection of the variables to be included in the final model.

A variable selection method for regression models should find one or more subsets of variables having the optimal prediction performance. Sometimes, this prediction is not optimized during the process of variable selection, and testing for all potential subsets of variables is not possible. Consequently, suboptimal methods for variable selection are applied and the prediction performance of regression models is estimated separately.

We have modified and improved a method proposed in 2007 by Liebminger et. al. named FASS that combines forward variable selection and all subsets regression. In order to explore the properties of FASS, we fit different models by forward-stepwise regression, all subsets regression and FASS. We tested also the robustness of FASS method applying changes on the method for the selection of the best subset and varying the number of variables in the initial model. We compared all the models obtained and we observed a better resolution when applying the FASS methodology.

We performed these comparisons on a dataset with host genetic and immunological information of over 800 individuals from Lima (Peru) and Durban (South Africa) with HIV infection. This dataset includes around 500 variables that can be classified as information on HIV immune reactivity (around 400 predictive variables) and individual genetic characteristics (around 100 predictive variables).

Keywords

variable selection, regression

References

Cost-Effectiveness of HIV Tropism Testing to Inform Antiretroviral Treatment with Maraviroc

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Abstract. Diagnostic laboratory tests may add critical information to guide treatment and improve patient outcomes, but payers often question whether the value of the additional information provided by tests is justified by their costs. A transition probabilities Markov model is used to perform an economic evaluation by simulating a patient’s cohort travelling through defined health status until the time horizon is reached. The transition probabilities between health status are determined taking into account i) the accuracy of the laboratory diagnostic tests, ii) the prevalence of the tested characteristics and iii) the efficacy of the therapeutic strategies chosen based on the test result. Input data were derived from published clinical trials and observational cohorts. Economic costs were assessed from the National Health System payer perspective and are reported on a present-value basis with a 3 percent annual discount rate. We evaluated the stability of the results with changes in model inputs by means of sensitivity analyses.

This analytical model was applied to elucidate whether co-receptor testing is cost-effective to determine patient’s suitability to benefit from the use of an antiretroviral treatment that includes maraviroc. All HIV strains require binding to CD4 plus at least one of the 2 co-receptors CCR5 or CXCR4 to enter human cells. Some HIV can use both co-receptors, and some individuals have a mixture of strains. Only patients with exclusively CCR5-tropic HIV are considered eligible to use the CCR5 antagonist maraviroc. Both maraviroc and co-receptors testing are expensive.

We considered a cohort of 10,000 patients who travelled in sequences of 3 month transitions between the following health status: Undetectable Viremia, Detectable Viremia and Death, until 3 years or death is reached. Model results included the costs of each test alternative and incremental cost-effectiveness ratios (ICER). This economic evaluation of tests for co-receptor can guide their use in medical practice.

Keywords

health economics, cost-effectiveness, HIV, co-receptor testing
Semi-Competing Risks with Interval-Censored Intermediate Event

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Abstract. Semi-competing risks arise when subjects may experience an intermediate event and a terminating event, like recurrence and death in follow-up cancer studies. Both events can be observed in the same individual if the intermediate event occurs first, but the occurrence of the terminating event in first place precludes the occurrence of the intermediate event. Therefore, the time $T_1$ to the intermediate event is censored by $T_2$, the time to the terminating event. Often these events are related: we deal with a bivariate survival problem with dependent censoring.

When the interest relies on the terminating event, conditional models for $T_2$ given $T_1$ provide information on the effect of the intermediate event on the terminating event. However, when the goals rely on the association between $T_1$ and $T_2$ or on the estimation of the marginal distribution of the intermediate event, $T_1$, a semi-competing risks approach is more appropriate.

Fine et al. (2001) proposed a method for semi-competing risks data under the assumption of a Clayton’s copula model for the joint survival function of $T_1$ and $T_2$. In this work we extend this approach to the case where the intermediate event is interval-censored. We assess the performance of the proposed method by presenting simulated and real data examples.

Keywords

semi-competing risk, interval-censoring, bivariate survival

References

Reduced Rank Hazards Regression with Fixed and Time Varying Effects of the Covariates

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Abstract. Perperoglou et al. [1] introduced Reduced Rank (RR) Hazard Regression when modeling survival data with time-varying effects. The RR model extends Cox’s model by including a matrix $F$ of time functions that interact with the covariates $X$. Thus, the hazard for a patient $i$ is given as:

\[
h(t|X_i) = h_0(t) \exp(X_i \Theta F'(t_i))
\]

where $h_0(t)$ is the unspecified baseline hazards and $\Theta_{p \times q}$ is a matrix of coefficients. In (1) matrix $\Theta$ can be written as a product of two submatrices, $B$ and $\Gamma$ of sizes $p \times r$, $q \times r$, respectively, where $r$ is the rank of the model. The full model is specified when $r = \min(p, q)$ leading to a full rank matrix $\Theta = BF'$. However, when a lower rank $r$ is chosen the model has fewer parameters $r(p + q - r)$.

Here we extend this model to allow both for time varying and time fixed effects of the covariates. Such a model is written as:

\[
h(t|X_i) = h_0(t) \exp(X_i \Theta F'(t_i) + Z_i \xi)
\]

where $Z_i$ is a matrix of covariates that do not have a dynamic effect and $\xi$ is a vector of their corresponding coefficients. We will present the model and discuss ways to identify which covariates should be modelled as fixed and which as dynamic using landmark analysis [2].

Keywords

reduced rank, time varying effects, landmark analysis

References

A Nonparametric Approach for Estimating the Survival Functions from Case-Control Family Data

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\textbf{Abstract.} Consider data arise from a typical case-control family study where individuals with a disease under study (case-probands) are matched with individuals who do not have the disease (control-probands) on age at onset and age at censoring, respectively. In addition, age at onset or age at censoring and disease status is also observed for one relative of each proband. For example, case-probands are women diagnosed with breast cancer, control-probands are breast cancer free women, and information is collected also on their mothers. We provide a novel nonparametric estimators of the marginal and bivariate survival functions based on the kernel estimator of the conditional survival functions. The weak convergence of the proposed estimators will be presented along with variance estimates. Extensive numerical studies show that our proposed estimators perform very well in terms of bias.

\textbf{Keywords}

case-control family study, bivariate survival functions, right censoring, kernel estimation
Using Scan Statistics on Multiple Processes with Dependent Signals and Assessing its Distribution, with Application to Sequence Search Along the Genome

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Abstract. The attempt to locate sequences of interest along the genome is a familiar problem that is frequently confronted by genome researchers. The challenge here is to identify short intervals of nucleotides on the genome, within noisy and much longer sequences, such as genes. One example in which the problem occurs is the search for transcription factor binding sites within a group of functionally related genes. Another challenging example, which will be discussed here, is the search for intronic regions. Inference on the presence of intronic regions can be made based on continuous monitoring of expression level across the genomic sequence, using a tiling array experiment, which can facilitate detection of sudden changes or occurrences of expression. Here, we suggest using a scan statistics to test whether an interval, within a specified gene, is showing the biological effect expected to occur in an intronic region. We offer a statistic that integrates several important considerations related to the dependence between adjacent measures of expression along the genomic sequence, and its effect on the FDR when testing simultaneously many random processes (genes). We also offer an analytical assessment of the scan statistics distribution considering this dependence under a normal stochastic process.
Building Maintenance: A Time-to-Event Approach and a Simulation Study

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Abstract. Decisions about intervention in existing buildings are generally based on information gathered from inspections, as a systematic tool for the identification of risk factors based on the characterization of the buildings, the building parts and elements that compose the façades and its materials, the injuries that may affect the façades, its severity, and finally, its magnitude. In this sense, in order to carry out an efficient preventive task and maintenance, knowledge of the evolution of injuries and their distribution is essential. However, this information, unfortunately, does not exist and there are few studies that describe the lifecycle of constructive elements in play; so we must use durability estimators based on inspections. The main problem of this methodology is the high variability of the resulting estimator. The goal of this presentation is to introduce a simulation study that aims to analyze this accuracy and allows the design of an efficient inspection plan.

Keywords

durability, maintenance, nonparametric estimator, simulation, survival analysis

References


The Use of Multi-State Models in the Analysis of Semi-Competing Risks Data

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Abstract. Semi-competing risks data arise, especially in medical research, when subjects are at risk of experiencing more than one event, one of which is terminal and one is not. For example, patients might be at risk of experiencing a terminal event (death from a specific disease) while simultaneously they are at risk of experiencing a competing event which is not terminal (stroke). As a result, if the non-terminal event occurs first then both events are potentially observable, subject to random censoring, and all the necessary information relevant for the estimation of the events distributions is available. When, however, the terminal event occurs first, this is no longer true since the observational process is terminated and the non-terminal event is being censored. As a result we have partial information for the estimation of the distribution of the non-terminal event. We investigate the use of multi-state models to analyze such data. We allow the presence of lost-to-follow-up as a distinct state in the model along with the transition states for the terminal and the non-terminal events. Due to lack of information, additional modeling assumptions are needed for fitting this model. Applications on the Whitehall II study on civil servants as well as on the CFAS longitudinal study of cognitive function are presented.

Keywords
multi-state models, semi-competing risks

References
Statistical Properties of Heterogeneity Measures in Meta-Analysis

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\textbf{Abstract.} In this work we consider three quantities that have been proposed as measures of the magnitude of between-studies heterogeneity in meta-analysis: the estimator of proportion of the total variance due to between-studies variability, $\hat{R_I}$; the similar descriptive statistic $I^2$; and the estimator of the between-studies coefficient of variation, $\hat{CV_B}$. Our goal is to develop and evaluate methods for computing the confidence intervals for these statistics. We test four bootstrap methods and propose eight new asymptotic methods for the calculation of confidence intervals. To illustrate the performance and to investigate these methods we provide an extensive simulation study, patterned from five published epidemiologic meta-analyses. Until now, no confidence intervals were available for statistics $\hat{R_I}$ and $\hat{CV_B}$ and this has limited the routine of their use. This new development should enhance the ability of investigators to assess heterogeneity in meta-analysis.

\textbf{Keywords}

meta-analysis, heterogeneity, confidence intervals

\textbf{References}


Inference in Generalized Linear Regression Models with a Censored Covariate

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Abstract. We study the problem of estimating the parameters in a generalized linear model when a covariate is subject to censoring. We propose a new method based on an estimating function approach. Our method does not assume a parametric form for the distribution of the response given the regressors and is computationally simple. In the linear regression case our approach implies the use of mean imputation of the censored regressor. We explore the use of flexible parametric models for the distribution of the covariate. We focus on survival time as the covariate subject to censoring and consider the use of the generalized gamma distribution, a platform distribution covering a wide variety of hazard rate shapes. Our method can be further robustified by considering models of nonparametric nature typically used in survival analysis such as the lognormal for the censored covariate. For models involving additional, fully observed, covariates we explore the use of a generalized gamma accelerated failure time regression model in which no parametric family assumption for the extra covariates is needed. Thus, our approach is broader than likelihood based multiple imputation techniques. Moreover, even in cases with a known parametric form for the response distribution, our method can be considered a feasible alternative to likelihood based estimation due to its computational simplicity. Simulation studies are conducted for continuous, binary and count data to evaluate the performance of the proposed method. We present an application using a well known real data set regarding primary biliary cirrhosis patients.

Keywords
accelerated failure time model, censored covariate, estimating functions, generalized gamma distribution, generalized linear model

References
An Efficient Algorithm to Perform Multiple Testing in Epistasis Screening

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Abstract. Research in epistasis or gene-gene interaction detection for human complex traits has grown exponentially over the last few years. It has been marked by promising methodological developments, improved translation efforts of statistical epistasis to biological epistasis and attempts to integrate different omics information sources into the epistasis screening to enhance power. The quest for gene-gene interactions poses severe multiple-testing problems. In this context, the maxT algorithm [Westfall&Young 1993] is one technique to control the false-positive rate. However, the memory needed by this algorithm rises linearly with the amount of hypothesis tests. In main-effects detection, this is not a problem since the memory required is thus proportional to the number of SNPs. In contrast, gene-gene interaction studies will require a memory proportional to the squared amount of SNPs. A genome wide epistasis analysis would therefore require $O(10^{12})$ memory, i.e. expressed in terabytes. Hence, cache problems are likely to occur, increasing the computation time. In this work we present a new version of maxT, requiring an amount of memory independent from the number of genetic effects to be investigated. This algorithm was implemented in our epistasis screening software MB-MDR-2.6.0 and applied to genetic data for Crohn’s disease, an inflammatory disease of the intestines. Refer to [Cattaert et al 2010] for more details about MB-MDR.

Keywords
epistasis, multiple testing, MAXT, MB-MDR

References
Marginal Structural Models
Under Different Mechanisms of Missingness

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Abstract. The aim of this study was to assess the performance of the Marginal Structural Models (MSMs), focusing mainly on use of the Last Observation Carried Forward (LOCF) to fill in missing values. Various scenarios of incomplete marker’s measurements were examined. We generated 1000 datasets of 1000 individuals with longitudinal data (12/year for 2 years). A normally distributed continuous marker was generated as a function of the counterfactual survival time $T_0$. Treatment initiation was a function of the marker’s value at each occasion. The actual survival time was produced as a function of $T_0$, the time of treatment initiation and the prespecified marginal treatment’s effect, $\psi$, which was chosen to be -0.80. When the full data were used, estimation of $\psi$ was almost unbiased, with relative bias 2.2% and corresponding mean coverage probability (cp) 95%. In case of a missed visit, which corresponds to no marker’s measurement and no treatment administration, estimation of the marginal treatment effect was fairly robust, even in case of 40% informative missingness, yielding a relative bias equal to 2.5% and mean cp 94%. In case of missingness on the confounder only, relative bias was affected by both the percentage and the mechanism of missingness. More specifically, for 25% and 50% MCAR, bias was 3.8% and 6.2%, while for the same percentages of MAR, bias was 7.6% and 13.2%, respectively. When the missing mechanism was informative, for 25% and 50% missingness, bias was increased to 17.1% and 18.6%, respectively. In this latter case, mean cps were also affected (75.1%- 84.6%). Imputation of the missing values using the predicted values from a linear mixed effects (LME) model reduced bias and increased the cps only in case of MCAR.

The above presented results imply that MSMs are robust in case of unequal time intervals between visits, even if these imbalances result from a non-ignorable mechanism. However, missing confounder values leads to biased estimates of treatment’s causal effect. In such a case, alternative to LOCF imputation methods must be considered.

Keywords
causal, marginal structural models, missing
Spatio-Temporal Analysis of Breast Cancer Mortality Risks

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Abstract. In recent decades, a decline in breast cancer mortality has been observed across Europe, and also in Spain. Our objective is to assess the spatio-temporal pattern during the period 1975-2005 by specific age groups (<45, 45 – 64, >65) in the Spanish provinces. For each age group, a spatio-temporal P-spline model is used to smooth the mortality risks. Smoothing is carried out in three dimensions: longitude, latitude, and time, allowing for a different time evolution of both spatial components. The age-specific decline is calculated as the maximum of the estimated curve in each province. A confidence band for each curve is also provided. For the first age group (<45), the decline in the different provinces is observed between 1986 and 1991. For women aged between 45 to 64 years, the change occurs between 1990 and 1993. For the third age group (>65), change points range from 1992 to 2000, unlike Malaga and Cadiz where the change has not been observed in the studied period. Northern and some Mediterranean provinces are the areas with higher mortality risks for all the age groups. The decline of mortality is delayed for the oldest age group. Province differences in the implementation of screening programs could explain some of the observed differences.

Keywords
mortality risks, p-spline model

References
Marginal Distribution Estimation from Double-Sampled Competing Risks Data

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Abstract. In semi-competing risks data, a terminal event censors a non-terminal event, but not vice versa. While estimation of the marginal distribution of the terminal event can be effectively conducted using the well-known Kaplan-Meier method, model-based approaches are usually necessary to estimate the marginal distribution of the non-terminal event when the two types of events are correlated. If the two-types of events can censor each other, the resulting data are competing risks data. In this case, it is well known that the marginal distributions of neither types of events are identifiable.

We consider a situation when obtaining the terminal event information from subjects who experienced non-terminal events can be costly and therefore are ascertained only on a subset of such subjects. An estimation procedure is proposed to deal with such data. Performance of the proposed method is demonstrated via asymptotic study, simulations, and real data analysis. We also consider related design issues and their applications on estimation of marginal distributions.

Keywords

competing risks, marginal distribution, double sampling, copula model
Estimator for the Correlation of Recurrent Events in Comparison to the Wei Lin and Weissfeld Method

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Abstract. Multiple endpoints are common in randomized clinical trials, and combining their analyses improves efficiency in evaluating treatment efficacy. To enable such analysis, the correlation between these endpoints has to be understood. This study focuses on the estimation of the correlation between two score statistics derived from bivariate survival data which follows Whitehead et al. (2010). The survival data are analyzed as interval-censored to determine the correlation, providing an accurate approximation to the correlation of the true logrank statistics. Assuming proportional hazards, the score statistic Z and Fisher’s information V are derived from a complementary log log approach. Conditioning on successive risk sets, the covariance between two such score statistics is obtained by summation of covariances. Data from a bladder cancer study are used for illustration, and replicated simulations to investigate the properties of the estimator and evaluate the accuracy of bivariate tests. Comparison with the method of Wei et al. (1989) is made. Our method uses the covariance of marginal statistics as we condition on successive risk sets, while WLW concerns the covariance of adjusted statistics and does not condition on risk sets. Extensive simulations show that our method is comparable to WLW.

Keywords

interval-censored, recurrent events, WLW

References


Bayesian Sample Size Estimates for One Sample Test in Clinical Trials with Dichotomous Outcomes

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Abstract. We present a Bayesian approach to sample size determination in binomial clinical trials. It uses exact methods and Bayesian methodology. Our sample size estimations are based on power calculations under the one-sided alternative hypothesis that a new treatment is better than a control by a clinically important margin. The method resembles a standard frequentist problem formulation and, in the case of conjugate prior distributions with integer parameters, is similar to the frequentist approach. We evaluate type I and II errors through the use of credible limits in Bayesian models and through the use of confidence limits in frequentist models. Particularly, for conjugate priors with integer parameters, credible limits are identical to frequentist confidence limits with adjusted numbers of events and sample sizes. We consider conditions under which the minimal Bayesian sample size is less than the frequentist one and vice versa.

Keywords

beta distribution, hypothesis, posterior distribution, prior distribution

References

Poster session
Analytic Approaches for Eye-Specific Outcomes: One Eye or Two?

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Abstract. The aim is to review the analytic approaches commonly used with eye-specific outcomes in clinical research recently published in ophthalmology journals and illustrate application of a simple hypothesis test for correlated binary outcomes. All 161 research articles published in five ophthalmology journals in the first two months of 2008 were initially considered. Publications were categorized according to the analytic approach: one eye selected, both eyes contribute or per-individual outcome. Studies were considered suboptimal when measurements from both eyes were included without inter-ocular correlation being considered or one eye was selected without description of a selection method. Four valid analytic approaches were compared using mild visual impairment (VI) prevalence data. Measurements from both eyes were included in 36 per cent of 117 studies. In 74 per cent of these there was no mention of possible correlation. Only 2 studies used statistical methods appropriate for correlated outcomes, and 6 more had a paired-eye design. In 29 per cent, one eye was selected: in 32 per cent the selection criteria were not stated. Sixty seven per cent of the articles contained only univariate comparisons. The main characteristics of the 47 suboptimal studies did not differ from the remaining studies. Using a test appropriate for correlated mild VI data resulted in a p-value 3.5 times that obtained ignoring the correlation. We conclude that between-eye correlation seems not to be commonly assessed in ophthalmology publications, although its knowledge aids the choice of analytic approach when eye-specific variables are of interest. Statistical methods appropriate for correlated ocular outcome data are not being widely applied.

Keywords

correlated outcomes, ICC, ophthalmologic data

References

Confounding Techniques in Experimental Design: Results of an Experiment on *Aniba Rosaeodora* in the Central Amazon

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Abstract. Our research work is based on a real experiment on *Aniba Rosaeodora* in the Central Amazon, under a reforestation program. A Factorial Block Design with Confounding was used to compare the behaviour of three different fertilizers, nitrogen, phosphorus and potassium. For the three fertilizers three different levels were considered and the experiment was located in the region of Maués-AM-Brazil. On computations we used SAS and language R, mainly the package agricolae. The results analysis indicate that the experimental technique was effective in discriminating between the fertilizers and at the same time it allowed to reduce the experimental area and the cost of deployment.

Keywords

experimental design, confounding, factorial block designs, reforestation

References


Visualization in Joint Regression Analysis Using R

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Abstract. Joint Regression Analysis (JRA) is a technique with great applicability for the comparison and selection of genotypes. The JRA technique consists in the adjustment of linear regressions of the yield of each genotype in their environmental index using Zig-Zag algorithm. After obtaining the adjusted coefficients, we can use the Upper Contour Method, which show the genotypes belonging to that contour, in a certain range of environmental indexes. After application of JRA, based in Oliveira(2008), we develop procedures and a program in R language that allows obtaining the Upper Contour, visualization of that contour and dominant genotypes at a range of environmental indexes. An application to a real data set of oat yield is presented.

Keywords

joint regression analysis, visualization, upper contour method, genotypes

References

A GEE Approach for Poisson Correlated Data

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Abstract. Clustered or correlated samples of categorical response data arise frequently in many fields of application. Longitudinal studies emerge when this clustering result from repeated measurements of individuals over time. Repeated measures studies, and in particular longitudinal studies, are important tools in epidemiological, clinical and social science research. The method of generalized estimating equations (GEE) introduced in Liang and Zeger (1986) is often used to analyze this type of data. This approach consists of two estimation steps. One is a quasi-likelihood method for estimating regression parameters which characterize the dependence of outcomes on the covariates. The other is a robust moment method for estimating correlation parameters which incorporates the dependence among outcomes. The estimation of correlation parameters is based upon the Pearson residuals. Park et al. (1998) considered a modification of the GEE approach using the Anscombe residual and the deviance residual. In this work, we propose to extend this idea to a family of generalized residuals. Finally, a simulation study is carried out to compare the performances of the new methods with the classical GEE for Poisson correlated outcomes.

Keywords

generalized estimating equation, generalized residuals, Poisson correlated data

References


Spatial-Mathematic Methods for Analysis of Indicators of Mortality

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Abstract. Analysis of indicators of mortality for all causes of mortality in different geographic regions, sex or other socio-economic characteristics could be useful for administrative and scientific reasons. There is a huge interest in calculating rightly the different and various indicators of mortality, for public health, both qualitatively and quantitatively, as well as their modeling and the use of these estimations in planning of public health. The study of mortality indicators is of high importance, specifically when we study them in different geographic fields and different units of time. In the present study, a certain methodologies are applied, which are able to be used in estimating the epidemiologic interpretation and the decision - making in public health. Material and Methods: The data that were used for the analysis of this particular work have been found by the Greek Statistical Service (GSS). These elements are about deaths per sex, age-related team and causes of mortality per prefecture of Greece during the years 2001 and 2006 as well as social - economic factors per prefecture. The coding of death causes was fulfilled by ICD 10 and afterwards these causes of mortality were grouped according to the teams of G27, totally 65 causes of mortality. The population of G27 was chosen for standard distribution. Finally, these indicators were grouped by CLUSTER ANALYSIS (K-MEANS). Placing, as objective, the Qualitative study with techniques of quantification (Mathematic or Statistical), in the analysis of territorial data, is specifically placed the following question, if the under examination phenomenon is able to be approached meditatively, and then the results of such an analysis of data (which immediately answer in the functional definitions) be able to create an explanatory frame or at list a sort of modeling, which will give as a result, algorithms. If the study via stochastic processes is not possible, a question of ascertainmen of nature of deterministic system is placed, and this is implied. It’s linear or non linear structure places a question of high importance. And this is due to the fact that, mainly the not linear systems of spatially distributed data mainly imitate the meditative origin data, fasmatically, statistically, analytically, etc. In order to give an answer to the above were mainly used METHODS OF SPATIAL STRUCTURE FUNCTION. For further study of dynamic nature of data, were used methods of ANALYSIS OF TOPOLOGIC VECTOR SPACES and TECHNIQUES arising from TENSOR CALCULUS. Results: Maps were made by the spatial program ArcGIS 9.2 and in these maps were portrayed the teams that were created by cluster analysis. Teams were created, based on standard indicators of mortality per sex, geographic region and year. It was found that the phenomenon (general indicator) is deterministic of low dimensionality, non linear and of strong spatial memory although it is not periodical as much for the year 2001 as for 2006.

Keywords spatial analysis, spatial structure function, spatial interpolation-Kringing, cluster analysis
Adaptive Hypothesis Multi-stage Phase II
Design for Time-to-Event Endpoint

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Abstract. The suggested phase II multi-stage designs for monitoring survival probabilities (Lin et al., 1996, Case and Morgan, 2003, Jennison and Turnbull, 2000) focus on testing the null hypothesis \(H_0: S(x) = S_0(x)\) versus the alternative \(H_A: S(x) > S_0(x)\) at significance level \(\alpha\) and power \(1 - \beta\) when \(S(x) = S_1(x)\), where \(x\) denotes the survival time of interest and \(S(.)\) denotes the survival function. In early phase clinical trials we often face the uncertainty of whether we have made the right choice for a specific target level \(S_1(x)\). For that purpose, an adaptive multi-stage procedure for evaluating survival probability is proposed that using the information of the previous stages, adjust the target survival level in each stage, while the type I error rate is controlled. This general hypothesis, also, creates confusion among clinicians and, in fact in many statisticians, since rejecting \(H_0\) and specifying \(S(x) = S_1(x)\) in power calculations cannot be considered equivalent that the survival probability of the particular therapy is greater than \(S_1(x)\). To address this issue, in the propose class of designs we test two hypotheses sequentially in each stage. In each stage, we first test the hypothesis \(H_{01}: S(x) \leq S_0(x)\) versus \(H_{A1}: S(x) > S_0(x)\). Only if this hypothesis is rejected we test the hypothesis \(H_{02i}: S(x) \geq S_i(x)\) versus \(H_{A2i}: S(x) < S_i(x)\) \((S_0(x) < S_i(x) < S_{i-1}(x) < S_1(x), i = 1,2,...,k - 1\), in order to examine if the therapy is effective enough to warrants further study. For the first stage we use an optimistic target level \(S_1(x)\) and for every other stage we test a less optimistic target level \((S_i(x) < S_1(x))\). Under specific upper bounds for the error levels, and the assumption that the accrual rate is fixed, we develop designs that minimize the expected study length (ESL).

Keywords

clinical trials, multi-stage design, adaptive design, time-to-event endpoint

References


Estimation of Catalan Breast Cancer Survival Functions, Corrected for Lead Time and Length Bias

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Abstract. The survival time of the screening-detected breast cancer (BC) cases are affected by lead time and length bias. The lead time bias occurs because of early diagnosis. Length bias arises because the tumors detected on screening examinations are more likely to have slower growth than the cases detected in the intervals between examinations and other groups of cancer cases not detected by screening. Different methodologies were used to estimate Catalan breast cancer survival functions free of lead-time and length biases. Data used were from Catalan cancer registries (Girona and Tarragona) and the Hospital del Mar early detection program. A simulation study was performed to reproduce the natural history of breast cancer and estimate early detection parameters. Screening-detected sojourn times and lead time estimates under different screening scenarios were obtained. Our results show the relevance of considering these biases when estimating survival.

Keywords
survival, breast cancer, early detection, lead time bias, length bias

References
Molecular and Epidemiological Characterisation of HIV-1 Infection Networks Involving Transmitted Drug Resistance Mutations in Northern Greece

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Abstract. The prevalence of TDR was estimated in 369 individuals who were diagnosed with HIV-1 infection in the period 2000 - 2007 at the National AIDS Reference Laboratory of Northern Greece. Phylogenetic analysis was performed with implementation of a maximum likelihood method on pol sequences. The overall prevalence of TDR in our population was 12.5% (9.1%, 15.8%), comprising 7.6% (4.9%, 10.3%) to nucleoside reverse transcriptase inhibitors (NRTIs), 5.4% (3.1%, 7.7%) to non-nucleoside reverse transcriptase inhibitors (NNRTIs) and 3.3% (1.4%, 5.1%) to protease inhibitors (PIs). Dual class resistance was identified in 3.8% (1.8%, 5.7%). Subtype A was the sole predictor associated with TDR (OR: 2.15, 95% CI: 1.10 to 4.19, p=0.025). Phylogenetic analyses, supported by bootstrapping >90% and genetic distance <0.015, revealed three transmission clusters involving drug resistant strains, including one cluster of 12 patients, 10 of whom were infected with a strain carrying both T215 revertant and Y181C mutations. Our findings underline the substantial impact of transmission networks on TDR in our population.

Keywords
HIV, subtype A, transmitted drug resistance, transmission clusters

References
Modelling Long-Term Trends in Cancer Mortality in Greece Using Joinpoint Regression

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Abstract. In modelling long-term trends in mortality or morbidity series of cancer, an important issue is the identification of the optimal number and position of change in rates cut-off points. The joinpoint regression program, provided by the U.S N. C. T., that implements a joinpoint regression model using a grid-search method to fit the regression function with unknown joinpoints, has been extensively applied. Its major limitation is that allows only for functions of time and therefore limits the investigation of other cofactors or effect modifiers. Using Greek cancer mortality data from 1968 to 2007 we applied several continuous and discrete distributions to analyse the trend either in standardised mortality rates or in counts, allowing for adjustment of confounders and/or for their interaction with time. Estimation of standard errors for the joinpoint models could be problematic due to the uncertainty created by the knot estimation. Here we applied several methods including the conditional variance and the jackknife estimation. Excluding naive standard error estimates of the parameters, all other methods gave similar results. For the modelling of age-standardised rates we propose to fit a piecewise linear regression on the log-scale in combination with the grid-search method for the estimation of the knots and with the jackknife method for the estimation of the adjusted standard errors. For count data we propose to fit a piecewise negative binomial model again in combination with the grid-search and the jackknife method. Results from the models on overall cancer mortality data among males indicated a statistically significant increase by 1.40% per year from 1968 to 1980, a non statistically significant increase by 0.06% from 1980 to 2000 and a statistically significant decrease by 0.73% per year from 2000 to 2007. There were statistically significant interactions between the age-groups and time. We intent to expand our methods to estimate, apart form the position, also the optimal number of knots and to test their performance when modelling outcome data with low counts.

Keywords

cancer mortality, count data, joinpoint regression
Development and Evaluation of an Entropy Index as a Gait Variability Measure in Orthopaedic Patients

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Abstract. Entropy is a concept associated with the state of any system, living or non-living. Entropy in essence is one way of defining and measuring sustainability, since it describes the degree of disorder or uncertainty in a system. If the degree of disorder is large (high entropy), then the system may not be sustainable. If entropy is low, sustainability is likely. Increasing entropy jeopardizes future sustainability [Shannon 1948, Tononi 1998].

People without kinetic problems control their gait and they produce bio-signals with periodical or almost periodical behaviour, which will be characterized by low entropy. On the other hand neuromuscular or musculoskeletal pathologies or injuries imply higher gait variability, producing more random bio-signals and therefore higher entropy [Tononi 1998]. In human movement, therefore it is possible to use entropy to measure instability in walking. Low entropy values reflect smooth, periodic, repeated movements. High entropy values are associated with the inability of a subject to repeat movements smoothly and regularly.

The proposed method consists of a tri-axial accelerometer sensor that was used for the gait measurement, and an entropy algorithm that was used to quantify the gait acceleration signal. Accelerometry is a low-cost and practical method of objectively evaluating human movements, with negligible effects on body behaviour. Acceleration of the body or individual body parts can be recorded within an exposure to any radiation, cost-effectively and objectively for subsequent analysis [Chen 2005, Culhane 2005]. The extension of Shannon’s entropy to continuous variables [Papoulis 1984], referred to as differential entropy and has never been previously used in orthopaedics. For this study we used a differential entropy algorithm to analyze and quantify the gait acceleration signal.

In this work we evaluate 1) how the entropic analysis of gait variability in two types of orthopaedic patients with MRI diagnosed conditions (lumbar spinal stenosis and anterior cruciate ligament deficiency) compares to those of healthy individuals and 2) the time course of these patients’ entropy from pre-op to 6 months after surgery.

Keywords

entropy, gait variability, anterior cruciate ligament, lumbar spinal stenosis, movement disorders
Effects of Antibiotics on MRSA Carriage Dynamics

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Abstract. Methicillin-Resistant Staphylococcus Aureus (MRSA) is a bacterium that is usually found on the skin and in the nose. Once it enters the body it becomes harmful as it is resistant to antibiotics and is one of the most serious causes of nosocomial and surgical site infections. In the project we are interested in assessing the effect of antibiotics of MRSA on data taken from a hospital study in London. A discrete-time Markov chain model is used to describe the daily MRSA carriage level in patients. One complication is that the carriage level is observed with error due to the swab tests’ sensitivity. We adopt a Data-Augmentation framework and then Bayesian inference for the model parameters is drawn via MCMC methods. We fit our model to the data obtained from the above study. Finally, we discuss how chi-square tests can be used to assess goodness-of-fit.

Keywords

Bayesian inference, MCMC, data augmentation, MRSA

References


Testing for a Changepoint in the Cox Survival Regression Model

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Abstract. The Cox regression model is a popular model for analyzing the effect of a covariate on a survival endpoint. The standard Cox model assumes that the covariate effects are constant across the entire covariate domain. In many epidemiological and other applications, there is interest in considering the possibility that the covariate of main interest is subject to a threshold effect: a change in the slope at a certain point within the covariate domain. In this paper, we discuss testing for a threshold effect in the case where the potential threshold value is unknown. We consider a maximum efficiency robust test (MERT) of linear combination form and supremum type tests. The simulation results suggest that the best overall choice of test statistic is a three-point supremum type test statistic. The sample size methodology will be useful in study planning.

Keywords

survival analysis, threshold, efficiency robust test, supremum test
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