PROGRAM SYMPOSIUM 2015

THURSDAY 15TH OF OCTOBER 2015

11:30-12:30 Welcome Coffee and snacks

12:30-12:40 Official opening of the meeting

12:40-14:20 Development and assessment of prediction models

- Ruth Pfeiffer (Bethesda, US): *An efficient procedure to combine biomarkers with limits of detection for risk prediction*
- Thomas Gerds (Copenhagen, Denmark): *Hazards for the heart and a PIM for the soul*

Coffee

14:40-16:20 Analysis of dynamic survival data

- Jan Beyersmann (Ulm, Germany): *Robust nonparametric estimation for multistate models*
- Per Kragh Andersen (Copenhagen, Denmark): *Pseudo-observations: A review*

Coffee

16:40-18:20 Causal effects and dynamic prediction

- Els Goetghebeur (Ghent, Belgium): *On covariate selection for dynamic prediction and causal questions*
- Bianca De Stavola (London, UK): *Current issues in mediation analysis*

19:00 Conference evening

FRIDAY 16TH OF OCTOBER 2015

9:00-10:40 Freiburg session

- Harriet Sommer: *The cure-death model - A new approach for a randomised clinical trial design to tackle antimicrobial resistance*
- Kristin Ohneberg: *Exposure density sampling: A promising approach of matching with respect to a rare time-dependent exposure*
- Nadine Binder: *Skimping on the number of follow-up visits? What's the bias and can we correct it?*
- Martin Wolkewitz: *A multi-state approach to unmask three common types of survival bias in a study about Tamiflu and mortality*

Coffee

11:00-12:40 Non-standard problems in survival analysis

- Ørnulf Borgan (Oslo, Norway): *Nested case-control studies: should one break the matching?*
- Maria Grazia Valsecchi (Monza, Italy): *Survival analysis with time-dependent treatments*

Lunch

13:30-15:10 Clinical relevance of omics-based predictors

- Harald Binder (Mainz, Germany): *Of mice and men: Integrating RNA-seq data for a translational perspective*
- Lisa M McShane (Bethesda, US): *Assessment of omics-based predictor readiness for use in a clinical trial*

ABSTRACTS

DEVELOPMENT AND ASSESSMENT OF PREDICTION MODELS

An efficient procedure to combine biomarkers with limits of detection for risk prediction

Ruth Pfeiffer

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Only a few procedures have been proposed so far that address how to combine information from multiple correlated markers that are also left and/or right censored due to lower or upper limits of detection. We extend dimension reduction approaches, specifically likelihood-based sufficient dimension reduction (LDR) to regression or classification with censored predictors. These methods apply generally to any type of outcome, including continuous and categorical outcomes. Using an EM algorithm, we find linear combinations that contain all the information contained in correlated markers for modeling and prediction of an outcome variable, while accounting for left and right censoring due to detection limits. We also allow for selection of important variables through penalization. We assess the performance of our methods extensively in simulations and apply them to data from a study conducted to assess associations of 51 inflammatory markers and lung cancer risk and build prediction models.

References

- Tomassi T, Forzani L, Bura E, Pfeiffer R, Sufficient dimension reductions for censored predictors, submitted.
- Cook RD, Forzani L, Likelihood-based sufficient dimension reduction, Journal of the American Statistical Association, 2009, 104 (485), 197-208.

Hazards for the heart and a PIM for the soul

Thomas Alexander Gerds

Section of Biostatistics, Department of Public Health, University of Copenhagen

Much of the last decade's cardiovascular research has focused on risk prediction. However, there is a risk of confusion and inappropriate use of the risk terminology, i.e., hazard risk, absolute risk, lifetime risk and competing risk, and unfortunately the same can be mentioned regarding the corresponding statistical methodology. A recent example of the confusion is the study of Demissei et al. (2014) [1] which concluded that it is not necessary to incorporate the competing risk of non-cardiovascular mortality into the SCORE model which predicts total cardiovascular risk. Indeed, one year earlier almost the same group of authors propagated the opposite conclusion that SCORE should account for non-cardiovascular mortality [2]. It is widely accepted that discrimination of a risk prediction model should be evaluated with the C-index. However, the literature is less clear about which C-index to use and how to estimate the different indices based on possibly right censored data and in the presence of competing risks. A probabilistic index model (PIM) is a regression model for the probability that one outcome exceeds another, see Thas et al. (2012) [3]. An attractive feature of a PIM is its interpretation. For example, the probability that one patient survives another patient can be linked to the differences in the risk factors of the two patients. In this talk I will work out the relation between PIM and C-index and use it to illustrate some features and limitations of risk prediction of cardiovascular events in the presence of non-cardiovascular mortality.

References

[1] Demissei, Postmus, Valente, van der Harst, van Gilst, Van den Heuvel, and Hillege. Should non-cardiovascular mortality be considered in the score model? Findings from the prevention of renal and vascular end-stage disease (prevend) cohort. European Journal of Epidemiology, published online, 2014.

[2] Demissei, Postmus, Gansevoort, van der Harst, and Hillege. Should non-cardiovascular mortality be The Competing Risk Eect of Non-Cardiovascular Mortality on Total Cardiovascular Risk Prediction: Non Cardiovascular Mortality Should Be Considered in the Systematic Coronary Risk Evaluation (SCORE) Model Proceedings of the 2013 annual meeting of the Netherlands Epidemiology Society. Volume 1 Issue S1 Abstract 44.

[3] Probabilistic index models (PIM) Thas, De Neve, Clement, and Ottoy. Journal of the Royal Statistical Society. B (2012) 74, pp. 623-671.

ANALYSIS OF DYNAMIC SURVIVAL DATA

Robust nonparametric estimation for multistate models

Jan Beyersmann

University of Ulm, Germany

Multistate models consider event histories as transitions (the events) between a finite number of states. We discuss some recent approaches to "robust" inference in situations where the standard nonparametric estimators may be hampered by too small risk sets in intermediate states or by possible violations of the common time-inhomogeneous Markov assumption. Our first motivating data example is a simple competing risks multistate model subject to left-truncation (delayed study entry). The data come from an observational cohort study on drug-exposed pregnancies. The aim was to quantify the absolute risk of adverse pregnancy outcomes such as spontaneous abortion. Because the time scale is gestational age and a spontaneous abortion may be precluded by an elective termination, the Aalen-Johansen estimator of the cumulative incidence function, allowing for left-truncation, was used. The result was that use of statin decreased the probability of an elective termination and increased the probability of life birth compared to a control group. The reason for this medically implausible finding was an early elective termination event when only three control women had entered the risk set. A stabilized estimator which discards contributions from random time intervals with too small risk sets overcomes this problem. The approach generalizes a proposal of Lai and Ying (Ann Stat 1991) for the Kaplan-Meier estimator. We will provide large sample results (improving some of the results of Lai and Ying) and discuss a subtle "condition on the future" issue. We will also argue that the approach is relevant for general multistate models in the absence of left-truncation, because intermediate states may display small risk sets, especially if the initial distribution is concentrated in one state. Next, we consider a competing risks approach to estimation of transition probabilities, revisiting a Kaplan-Meier-integral-based suggestion by Meira-Machado et al. (LiDA 2006). Exploiting Inverse Probability of Censoring Weighting on the plane, we find theoretically more efficient estimators, which by a data subsetting principle give rise to a class of transition probability estimators in general non-Markov multistate models. The latter approach uses consistency of the Aalen-Johansen estimator of state occupation probabilities even in non-Markov models, if censoring is entirely random (Datta and Satten, Stat Prob Lett, 2001). We also revisit the approach of Datta and Satten, improving on some of their martingale-based arguments and also allowing for left-truncation. Results will be illustrated in simulations and real data analyses.

Pseudo-observations: A review

Per Kragh Andersen

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Pseudo-observations were introduced as possible outcome variables in regression models for censored event history data by Andersen, Klein & Rosthøj (Biometrika, 2003). Since then, the method has been expanded and applied in a number of settings, including restricted mean life time, competing risks (Klein & Andersen, Biometrics, 2005) and the t-year survival probability. The theoretical foundation was laid by Graw, Gerds and Schumacher (LIDA, 2009) and further developed more recently by Jacobsen and Martinussen.

Thus, the method is now rather well established and partly implemented in both R, Stata and SAS. This development will be reviewed and exemplified with data from bone marrow transplantation and other studies and open problems will be discussed.

CAUSAL EFFECTS AND DYNAMIC PREDICTION

On covariate selection for dynamic prediction and causal questions

Els Goetghebeur

Ghent University

Survival prediction from a target exposure variable and potential confounders forms an important tool when estimating the causal effect of exposure in the traditional way as well as through structural models. When expensive covariate measurements could be taken it begs the question whether we should obtain them for cost effective prediction and if so, when and how often they are best measured. In this talk we look at landmark analysis for updating causal effect measures over time.

Our task is twofold: 1) to adapt landmark analysis to produce updated dynamic predictions under causal interventions and 2) to consider cost efficiency of the incorporation of expensive covariates at onset and repeatedly over time. The ultimate goal thereby is to usefully evaluate what is expected to happen under specific interventions in different population strata, to optimize stratum-specific choices and thus provide guidance for public health decisions. We focus on two applications: estimating the evolution in hospital specific quality of care over time and the dynamic prediction of survival time from a cohort of biobank participants with updated biomarker measurements.

References

- Fouskakis D. and Draper D. Comparing stochastic optimization methods for variable selection in binary outcome prediction, with application to health policy. JASA, 2008.
- Danaei G. et al., Observational data for comparative effectiveness research: An emulation of randomised trials of statins and primary prevention of coronary heart disease, SMMR 2013.
- Parast L.; Tian L. and Cai T. Landmark Estimation of Survival and Treatment Effect in a Randomized Clinical Trial. JASA, 2014.
- Van Rompaye B., Eriksson M. and Goetghebeur E., 2015: Evaluating hospital performance based on excess cause-specific incidence. Statistics in Medicine, 2015

This talk refers to joint work with Alina Nicolaie, Machteld Varewyck and Stijn Vasteelandt.

Current issues in mediation analysis

Bianca L De Stavola

London School of Hygiene and Tropical Medicine

In diverse fields of empirical research attempts are made to decompose the effect of an exposure on an outcome into its effects via a number of different pathways. Path analysis has a long tradition in dealing with enquiries of this sort, but more recent contributions in the causal inference literature have led to greater understanding of the statistical estimands for these pathway-specific effects, the assumptions under which they can be identified, and statistical methods for doing so.

However the majority of causal inference contributions has focused on settings with no intermediate confounders (i.e. confounders of the mediator-outcome relationship on the causal pathway from the exposure) and considers only partitioning the total effect of an exposure into the components that involve or do not involve a single mediator. These restrictions are very limiting in mediation studies applied to life course epidemiology, where intermediate confounding is the norm, or to studies involving multiple biomarkers as mediators, now increasingly common in the OMICS era.

This talk will discuss extensions to these settings using examples taken from a life course study of eating disorders in girls and one of metabolomic mediators in a genetic study of cardiovascular risk.

This work is in collaboration with Rhian Daniel (LSHTM), Juan-Pablo Casas (LSHTM) and Nadia Micali (UCL).

References

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- VanderWeele T, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. Statistics and its Interface. 2009;2:457-468.

FREIBURG SESSION

The cure-death model - A new approach for a randomised clinical trial design to tackle antimicrobial resistance

Harriet Sommer

On behalf of COMBACTE consortium
Institute for Medical Biometry and Statistics, Medical Center - University of Freiburg (Germany)

Antimicrobial resistance (AMR) is a growing problem worldwide and with few new drugs making it to the market there is an urgent need for new medicines to treat resistant infections. There is a variety of primary endpoints used in studies dealing with severe infectious diseases,

recommendations given by the existing guidelines are not consistent nor is their practical application. Usually patients' cure rates are compared in trials dealing with AMR but they often suffer from severe diseases besides their infection, so mortality shall not be disregarded. A mortality rate of about 10% until 30% can be assumed within 30 days.
To understand the etiological process how the new treatment influences the cure process, we propose to perform a joint model with two primary endpoints – a combination of non-inferiority study regarding mortality and superiority study concerning cure using a multistate model where death without previous cure acts as competing event for cure and vice versa.
Mostly, patients die due to the underlying disease and even if the infection can be considered as cured, patients can die nevertheless. By means of analogies coming from oncology, the model has to be extended to an illness-death model (here referred to as cure-death model), a special case of a multistate model [Schmoor et al., 2013].

Applied to real data examples, as e.g. the Ceftobiprole trial by Basilea [Awad et al., 2014], and simulated data, we compare the simple competing risks model with the cure-death model and show that mortality after being cured cannot be ignored either.

References:

- Schmoor C, Schumacher M, Finke J, Beyersmann J. Competing risks and multistate models. Clinical Cancer Research 2013; 19(1):12-21
- Awad SS, Rodriguez AH, Chuang YC, Marjanek Z, Pareigis AJ, Reis G, et al. A phase 3 randomized double-blind comparison of Ceftobiprole Medocaril versus Ceftazidime plus Linezolid for the treatment of hospital-acquired pneumonia. Clinical Infectious Diseases 2014; 59(1):51-61

Exposure density sampling: A promising approach of matching with respect to a rare time-dependent exposure

Kristin Ohneberg

Cohort sampling designs like a nested case-control or case-cohort design are an attractive alternative to a full cohort analysis, especially in the situation where the event of interest is rare and the collection of covariate information is expensive. These cohort sampling designs require much less resources, while they are sufficient to provide results comparable to the analysis of the full cohort. For nested case-control studies incidence density sampling is applied, where controls for each case are randomly selected from the individuals at risk just prior to the occurrence of a case event. Incidence density sampling hence yields a dynamic matching with respect to an observed outcome. If interest is in the impact of a rare time-dependent exposure on the time until some specific endpoint, a dynamic matching with respect to exposure occurring over time is required. For this purpose exposure density sampling has been suggested as an efficient sampling method (Wolkewitz et al., 2009). The resulting sub-cohort may save resources if exposure and outcome data are available for the full cohort but additional covariate information is required that is rather costly or time-consuming to obtain. For some simplistic scenarios, exposure density sampling has shown to yield unbiased results. Yet the analysis investigated so far considered constant hazards and resetting the entry time, the latter being reasonable for exposed individuals, but probably less adequate for the unexposed individuals. Our aim is to further examine exposure density sampling and alternative methods of analysis (Savignoni et al., 2014) in a clinical cohort of women after breast cancer treatment where interest is in the effect of a subsequent pregnancy.

References

- Savignoni, A., Giard, C., Tubert-Bitter, P., and De Rycke, Y. (2014). Matching methods to create paired survival data based on an exposure occurring over time: a simulation studywith application to breast cancer. BMC Medical Research Methodology, 14:83.
- Wolkewitz, M., Beyersmann, J., Gastmeier, P., and Schumacher, M. (2009). Efficient risk set sampling when a time-dependent exposure is present: matching for time to exposure versus exposure density sampling. Methods Inf Med, 48:438-443.

Skimping on the number of follow-up visits? What's the bias and can we correct it?

Nadine Binder

In epidemiological studies information on disease status can often only be collected at a few discrete follow-up times, often after some years. This can be done only retrospectively in individuals who are alive at follow-up, but the information will be missing for those who died between two visits. Right-censoring the death cases at the last visit (ad-hoc survival analysis) generally underestimates the disease incidence [1], resulting in biased hazard ratio estimates, but in both directions [2]. In practice, the problem is hardly recognized and not explicitly addressed in reporting guidelines, e.g., the STROBE statement. In a systematic literature survey considering six representative journals, we investigated the prevalence of cohort studies susceptible to this bias, and we will illustrate by means of some examples to which extent the problem is discussed in subject-matter publications. Since the observed data actually has underlying illness-death structure, we furthermore investigated to which extent three approaches based on multi-state models [1,3,4], taking the death cases into account, provide less biased hazard ratio estimates. While in simple simulation studies all approaches were seen to work well, only the imputation based approach provided unbiased results in a real data example where missing disease information was artificially induced to compare the results with those from the full cohort.

References

[1] Joly P, Commenges D, Helmer C, Letenneur L (2002). A penalized likelihood approach for an illness-death model with interval-censored data: application to age-specific incidence of dementia. Biostatistics 3(3):433-43.
[2] Binder N, Schumacher M (2014). Missing information caused by death leads to bias in relative risk estimates. J Clin Epidemiol 67(10):1111-20.
[3] Leffondré K, Touraine C, Helmer C, Joly P (2013). Interval-censored time-to-event and competing risk with death: is the illness-death model more accurate than the Cox model? Int J Epidemiol 42(4):1177-86.
[4] Yu B, Saczynski JS, Launer L (2010). Multiple imputation for estimating the risk of developing dementia and its impact on survival. Biom J 52(5):616-27.

A multi-state approach to unmask three common types of survival bias in a study about Tamiflu and mortality

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Summary

"Skin cancer improves survival" (International Journal of Epidemiology, 2014), "Oscar winners live longer than nominees" (Annals of Internal Medicine, 2001): such results have been shown to be subject to time-dependent bias. These apparent effects disappear if the time-dependent exposure (skin cancer, Oscar winning) is treated as an time-dependent covariate.

Time-dependent bias has also been discussed in a recent study claiming that the swine-flu drug Tamiflu reduced mortality [1,2]. Since only hospitalized patients are observed, two other types of survival bias might occur in addition. First, hospital admission is usually a few days after influenza onset; ignoring this external left-truncation in the analysis may lead to length bias. Second, discharged patients cannot simply be handled as censored since they are usually in a better health condition than hospitalized patients; they should be handled as competing events. Classical survival models such as Kaplan-Meier curves fail to address these issues. We use the FLU-CIN data [3], the British part from the international meta-analysis [1]. Based on this data, we propose a multi-state model (onset, admission, treatment, discharge and death) to investigate the impact of bias due to ignoring the time-dependency of treatment, left-truncation and competing events. The impact differs in magnitude and direction and will be displayed in isolation as well as in combination.

Key words
multi-state model, competing risks, time-to-event analysis, time-dependent bias, length bias, competing risk bias

References:

[1] Muthuri SG, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Resp Med 2014;2:395-404.
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[3] Myles, PR, et al. (2012). Predictors of clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1 pandemic 2009-2010 in the UK. Thorax, 67, 8:709-17.

NON-STANDARD PROBLEMS IN SURVIVAL ANALYSIS

Nested case-control studies: should one break the matching?

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In a nested case–control study, controls are selected for each case from the individuals who are at risk at the time at which the case occurs. We say that the controls are matched on study time. To adjust for possible confounding, it is common to match on other variables as well. The standard analysis of nested case-control data is based on a partial likelihood that compares the covariates of each case to those of its matched controls. It has been suggested that one may break the matching of nested case-control data and analyse them as case-cohort data using an inverse probability weighted (IPW) pseudo likelihood. Further, when some covariates are available for all individuals in the cohort, multiple imputation (MI) makes it possible to use all available data in the cohort. In the talk, the standard method and the IPW and MI approaches will be reviewed, and the methods will be compared using simulations that cover a range of scenarios, including one and two endpoints.

[1] Borgan O, Keogh R (2015) Nested case-control studies: should one break the matching?. Lifetime Data Analysis 21(4):517-41

Survival analysis with time-dependent treatments

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The absolute measure of the cumulative probability of survival with the Kaplan-Meier estimator is still the most used quantity when describing the outcome of different treatment options. However, when an intervention may occur at different times from the starting point of observation, the Kaplan-Meier estimator generally yields to biased results if the intervention is considered fixed at that point. We discuss the issue of an appropriate graphical representation of survival in the presence of a time dependent treatment change accounting for different timescales. We consider both a non-parametric approach and a parametric approach based on the use of a multiple timescale model. This model is also shown to provide, in the presence of a time dependent intervention, an estimate of treatment effect in terms of hazard ratios by flexible modelling and a valid prediction tool in terms of estimate of prognosis for a given patient whose initial treatment might change later in time. In particular, the comparison of chemotherapy versus transplant in children with high-risk acute lymphoblastic leukemia in first remission will be used as an example.

References

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CLINICAL RELEVANCE OF OMICS-BASED PREDICTORS

Of mice and men: Integrating RNA-seq data for a translational perspective

Harald Binder

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Next Generation Sequencing (NGS) techniques allow for RNA-seq measurement of gene expression with an unprecedented resolution. Corresponding fine grained data analysis and modeling challenges bioinformatic and statistical approaches. Two main areas of application, carefully controlled experiments with model organisms and clinical cohorts, have received much attention in the methods communities, and led to two distinct kinds of approaches for data analysis. Experimental data are primarily characterized by a small number of biological replicates, requiring careful statistical testing [1]. Clinical cohort data call for risk prediction models, e.g. fitted by regularized multivariable regression techniques [2]. Statistical tools that link these two kinds of approaches can provide a building block for translation from model organisms to patients. As an example, I will consider RNA-Seq data from a mouse tumor model that is to be linked to human data from the Cancer Genome Atlas (TCGA). The relatively large sample size in the latter source enables multivariable modeling for taking correlation and biological network structure into account. Specifically, regularized regression is used to obtain gene weights. These are integrated into statistical testing for the mouse data to enrich the top list of differentially expressed genes with those genes that are also relevant in clinical cohorts.

Selection of weighting schemes and potential power gains are investigated. The results highlight that bioinformatic and statistical approaches for integrating RNA-Seq data from model organisms and clinical cohorts can considerably improve analysis of experiments while at the same time enabling a translational perspective.

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Assessment of omics-based predictor readiness for use in a clinical trial

Lisa M McShane

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Successful translation of omics-based assays into clinically useful tests requires effective collaboration among scientists representing multiple areas of expertise relevant to 'omics'-based test development. The US National Cancer Institute has developed a checklist of criteria that can be used to determine the readiness of an omics-based test for guiding patient care in clinical trials [1-2]. The checklist criteria cover issues relating to specimens, assays, mathematical modeling, clinical trial design, and ethical, legal and regulatory aspects. The checklist is intended as an aid to investigators developing omics tests to guide them toward best practices, make them aware of common pitfalls in development, and enhance the reliability, reproducibility, and usefulness of omics research. The checklist will be used to evaluate proposals for NCI-sponsored clinical trials in which omics tests will be used to guide therapy.

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