MEDICAL UNIVERSITY OF VIENNA | Medizinische Universität Graz | IDEAS Improving drug development | I B R O e S

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Einladung zum Seminar

des Zentrums für Medizinische Statistik, Informatik und Intelligente Systeme (MUW),
des Instituts für Med. Informatik, Statistik und Dokumentation (MUG),
der Wiener Biometrischen Sektion (WBS) und
der Biometrischen Sektion Steiermark-Kärnten (BSSK) der Internationalen Biometrischen Gesellschaft (IBS),
Region Österreich – Schweiz (ROeS)
Gemeinsam mit IDEAS ITN[1] organisiert.

Organisatoren: Andrea Berghold, Franz König, Nicolas Ballarini
Datum & Zeit: Donnerstag, 29 November 2018, 12:30 - 16:00 Uhr
Ort: Jugendstilhörsaal, Medizinische Universität Wien
Bauteil 88 – Ebene 3, Spitalgasse 23, 1090 Wien
Plan siehe: http://bit.ly/jugendstilhoersaal

AGENDA

12:30 – 14:00 Session 1:

- Keynote: Thomas Jaki (Lancaster University): The IDEAS network: Training and research under one umbrella
- Andreas Gleiß (MUW): Quantifying degrees of necessity and of sufficiency in cause-effect relationships with dichotomous and survival outcomes
- Edith Hofer (MUG): Genome-wide association study of cortical thickness, surface area and volume
- Sonja Zehetmayer (MUW): A new omnibus test for the global null hypothesis

14:00 – 14:30 Kaffeepause

14:30 – 16:00 Session 2:

- Alexander Avian (MUG): Scaling properties of pain intensity ratings in paediatric populations using the Faces Pain Scale-revised
- Susanne Strohmeier (MUW): Time-dependent mediators in survival analysis: Modeling direct and indirect effects with the additive hazards model
- Susanne Urach (MUW): Testing endpoints with unknown correlation
- Michael Kammer (MUW): Combining dynamic Cox prediction models and the Lasso
- Nicolas Ballarini (MUW): Graphical approaches for subgroup analysis in clinical trials

Wir freuen uns über eine rege Teilnahme am Seminar.

Registrierung: http://bit.ly/2018herbstseminar

[1] The IDEAS project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567

ABSTRACTS

12:30 - 13:06

The IDEAS network: Training and research under one umbrella

Thomas Jaki

Drug development is a long and costly process which suffers from the major shortcoming that frequently failure is often only determined during the final stage. Advanced statistical methods for study design, evaluation and analysis, employed already at the early phases of drug development, have a great potential to increase the efficiency of the development process.

IDEAS is a European training network for 14 early stage researchers working on statistical methods for early drug development. The network is funded by the European Union's Horizon 2020 research and innovation programme and comprises of 8 full partners and three associated partners at major European universities, the pharmaceutical industry, and consulting companies.

In this talk I will outline the structure of IDEAS and then discuss one of the research projects undertaken within the programme. More specifically I will discuss a design proposal that adaptively seeks to maximise the expected number of successes (ENS) while maintaining good power.

13:06 - 13:24

Quantifying degrees of necessity and of sufficiency in cause-effect relationships with dichotomous and survival outcomes

Andreas Gleiss, Michael Schemper

We suggest measures to quantify the degrees of necessity and of sufficiency of prognostic factors for dichotomous and for survival outcomes. A cause, represented by certain values of prognostic factors, is considered necessary for an event if, without the cause, the event cannot develop. It is considered sufficient for an event if the event is unavoidable in the presence of the cause. Necessity and sufficiency can be seen as the two faces of causation, and this symmetry and equal relevance are reflected by the suggested measures. The measures provide an approximate, in some cases an exact, multiplicative decomposition of explained variation as defined by Schemper and Henderson for censored survival and for dichotomous outcomes.

The measures, ranging from zero to one, are simple, intuitive functions of unconditional and conditional probabilities of an event such as disease or death. These probabilities often will be derived from logistic or Cox regression models; the measures, however, do not require any particular model.

The measures of the degree of necessity implicitly generalize the established attributable fraction or risk for dichotomous prognostic factors and dichotomous outcomes to continuous prognostic factors and to survival outcomes. In a setting with multiple prognostic factors they provide marginal and partial results akin to marginal and partial odds and hazard ratios from multiple logistic and Cox regression.

Properties of the measures are explored by an extensive simulation study. Their application is demonstrated by typical real data examples.

13:24 - 13:42

Genome-wide association study of cortical thickness, surface area and volume

Edith Hofer

Cortical thickness, surface area and volumes vary with age and cognitive function, and in neurological and psychiatric diseases. We examined genome-wide associations and genetic correlations of these cortical measures across the whole cortex, and in 34 anatomically predefined regions in a discovery sample of 22,822 individuals from 20 cohorts within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium. We identified 159 genome-wide significant associations and found genetic heterogeneity between cortical measures and brain regions.

13:42 - 14:00

A new omnibus test for the global null hypothesis

Sonja Zehetmayer

Global hypothesis tests are an important tool in the context of, e.g, clinical trials, genetic studies or meta analyses, when researchers are not interested in testing individual hypotheses, but in testing whether none of the hypotheses is false. There are several possibilities how to test the global null hypothesis when the individual null hypotheses are independent. If it is assumed that many of the individual null hypotheses are false, combinations tests (e.g, Fisher or Stouffer test), which combine data from several endpoints to a single test statistic, have been recommended to maximise power. If, however, it is assumed that only one or a few null hypotheses are false, global tests based on individual test statistics are more powerful (e.g., Bonferroni or Simes test). However, usually there is no a-priori knowledge on the number of false individual null hypotheses. We therefore propose an omnibus test based on the combination of p-values. We show that this test yields an impressive overall performance.

14:30 - 14:48

Scaling properties of pain intensity ratings in paediatric populations using the Faces Pain Scale-revised

Alexander Avian

The Faces Pain Scale-revised (FPS-r) has been developed as an interval scale. For other pain measurement instruments, several studies found evidence for and against an interval level of measurement. The primary aim of the current study was to evaluate the scale properties of the FPS-r using an item response theory approach. Within a secondary analysis of three models: the rating scale model (interval scale), the graded response model (no interval scale, ordered response categories) and the partial credit model (no interval scale) were used to scale the data. In all three studies, the rating scale model was outperformed by the graded response model or the partial credit model in terms of model fit. Overlapping response categories were found in items associated with less pain. Response category widths were wider for categories associated with low pain intensity and smaller for categories associated with high pain intensities. Smallest response categories were 1%–67% smaller compared to the widest response category of the same item. According to these findings, the interval scale properties of the FPS-r may be questioned. Item response theory methods may help to solve the problem of missing linearity in pain intensity ratings using FPS-r.

14:48 - 15:06

Time-dependent mediators in survival analysis: Modeling direct and indirect effects with the additive hazards model

Susanne Strohmaier, Mats J. Stensrud, Vanessa Didelez, Rhian Daniel, Kjetil Røysland, Odd O. Aalen

Causal mediation analysis for survival data is a challenging problem that gained increasing attention in the last decade, whereby properties of the additive hazard model proved particularly helpful. We emphasis a dynamic point of view, that is, understanding how the direct and indirect effects develop over time. Hence, importantly, we allow for a time varying mediator. To define direct and indirect effects in such a longitudinal survival setting we take an interventional approach (Didelez, 2018) where treatment is separated into one aspect affecting the mediator and a different aspect affecting survival. In general, this leads to a version of the non-parametric g-formula (Robins, 1986). We demonstrate that combining the g-formula with the additive hazards model and a linear structural equation model for the mediator process results in simple and interpretable expressions for direct and indirect effects in terms of relative survival as well as cumulative hazards. Our results generalise and formalise the method of dynamic path analysis (Fosen et al, 2006; Strohmaier et al, 2015) and also work by Lange and Hansen (2011). To illustrate the method we employed data from the Systolic Blood Pressure Intervention Trial (SPRINT), a randomized, controlled, multi-center trial that was originally designed to compare the effects of two different target values of systolic blood pressure on a composite cardiovascular outcome. We utilized the available repeated blood pressure measurements to address whether the reported increased risk of kidney injury or failure was mediated through diastolic blood pressure.

15:06 - 15:24

Testing endpoints with unknown correlation

Susanne Urach, **Franz König, Martin Posch**

As the correlation structure is usually unknown, multiple testing procedures of endpoints in confirmatory clinical trials often use conservative methods based on the marginal distributions of test statistics to strongly control the familywise type I error rate. Alpha exhaustive tests relying on the joint multivariate distribution either presume known correlations or use estimates based on the observed data. Calculating the critical boundaries under the assumption that the correlations are equal to some known values can lead to a type I error rate inflation in case of misspecification, the same is true if the correlations are estimated from the data and the sample size is low. We considered multiple testing procedures where the critical values are derived based on the assumption of multivariate normally distributed test statistics and quantified the inflation of the type I error rate due to assumed and estimated correlations. Furthermore, we apply the confidence interval approach by Berger and Boos to the two endpoint setting in order to deal with the unknown correlation and achieve strict type I error rate control for bivariate normally distributed test statistics. We improved Berger and Boos' method by deriving a sharper upper bound for the type I error rate increasing the power of the corresponding multiple testing procedure. The impact of using t-distributed instead of normally distributed test statistics is evaluated and respective adjustments are explored. The power of the methods assuming known correlation respectively estimating the correlation and the Berger Boos method are compared with non-parametric testing procedures in the setting with two endpoints.

15:24 - 15:42

Combining dynamic Cox prediction models and the Lasso

Michael Kammer, Georg Heinze

Dynamic Cox prediction models incorporate information on the current status of an individual to update predictions throughout follow-up. This is achieved by a series of ‘landmark’ models, each of which is incorporating covariate data up to a specific time point, the landmark. In each of those models, a covariate may have a different effect size.

Using a single Cox ‘supermodel’, smooth transitions between these landmark-specific effects can be assumed and estimated. Such a model offers a lot of flexibility and requires careful model selection, for example to control the way how effects are allowed to change over the landmarks. Our aim is to investigate how the Lasso can be applied in this situation to help with the process of selecting suitable model structures. We will discuss several challenges which arise when combining landmarking and the Lasso:

First, a pre-processed dataset for the landmarking approach contains dependent observations, as an individual will usually appear at several landmarks. How should we deal with these dependencies in Lasso coefficient estimation and tuning parameter selection?

Second, a Cox supermodel facilitates selection of effects at several layers of hierarchy. In some situations we may want to penalize the main and the time-varying effect of a covariate alike. Other situations may demand to only penalize the time-varying component. How can we apply the Lasso to penalize the total effect of a covariate or to only penalize changes in effects between landmarks?

Third, it may also be of interest to provide more penalization for changes in effects across landmarks than on the constant main effect over all landmarks. This may avoid overfitting the time-varying component of the effects, which could arise from decreasing sample sizes over time. How could this be incorporated into an analysis using the Lasso?

Using data from a study on dynamic prediction of venous thromboembolism, we will demonstrate how to implement these ideas in R with available software packages.

15:42 - 16:00

Graphical displays for subgroup analysis in clinical trials

Nicolas Ballarini, Yi-Da Chiu, Franz Koenig, Martin Posch and Thomas Jaki

Subgroup analyses are a routine part of clinical trials to investigate the effect of treatments in subsets of the population under study. The purpose of this assessment may be to ensure that there are no groups of patients for whom the treatment is harmful despite being effective in the majority of patients or to identify groups of patients that may benefit from a treatment when the overall effect is small or zero. Graphical approaches play a key role in subgroup analyses to visualize effect sizes of subgroups, aid identification of groups that respond differentially, and communicate the results to a wider audience.

However, many existing approaches do not capture the core information and/or are prone to lead to misinterpretation of subgroup effects. In this work, we critically appraise existing visualization techniques, propose useful extensions to increase their utility and attempt to develop an effective visualization approach. The graphical techniques considered include level plots, contour plots, bar charts, Venn diagrams, tree plots, forest plots, Galbraith plots, L'Abbé plots, the subpopulation treatment effect pattern plot, alluvial plots and UpSet plots. We illustrate the methods using a dataset of a treatment for prostate cancer with survival outcome.

IDEAS is a European training network for early-stage researchers working on statistical methods for early drug development. Drug development is a long and costly process which suffers from the major shortcoming that frequently failure is often only determined during the final stage. Advanced statistical methods for study design, evaluation and analysis, employed already at the early phases of drug development, have a great potential to increase the efficiency of the development process. IDEAS provides a tailored programme that includes specific training on quantitative methods for early drug development and generic skills for statisticians. The network takes a multi-national trans-sectoral approach that allows students to experience both academia and industry. This is achieved through joint supervision and a secondment scheme to the partner institution.

For more information on the ITN project and the research see:
http://www.ideas-itn.eu/

Or check out our Youtube channel for a summary of the research projects:
http://bit.ly/ideas_youtube