Seminar

Institut für Medizinische Informatik, Statistik und Dokumentation, MedUni Graz
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gemeinsam mit der

Wiener Biometrischen Sektion (WBS) und Biometrischen Sektion Steiermark-Kärnten (BSSK)

Mittwoch 2.12.2020 11:00-14:05

Ort: Webex, Zugang (direkt klicken oder in den Browser kopieren)

https://medunigraz.webex.com/medunigraz/j.php?MTID=m6ded47f91219e8b15e158059027efcb3

Session 1: 11:00-12.30

11:00-11:20 Josef Fritz and Hanno Ulmer (I):
Mediation analysis with multiple mediators: a case study

11:20-11.40 Mariella Gregorich (W):
Subject-specific Networks as Predictive Features for Prognostic Modelling - A Scoping Review

11:40-12:00 Bastian Pfeifer (G):
A hierarchical clustering and data fusion approach for disease subtype discovery

12:00-12:20 Michael Kammer (W):
Evaluating selective inference for the Lasso: a comparative simulation study and practical considerations

Session 2: 12:45-14:05

12:45-13:05 Michael Edlinger (I):
Risk prediction models for discrete ordinal outcomes: calibration and the impact of the proportional odds assumption

13:05-13:25 Alexander Avian (G):
How to maximize and minimize response rates in online surveys

13:25-13:45 Robin Ristl (W):
Testing procedures for the comparison of multiple characteristics of different survival functions

13:45-14:05 Elias Meyer (W):
Designing and simulating exploratory platform trials

Abstracts

Session 1

Mediation analysis with multiple mediators: a case study

Josef Fritz, Hanno Ulmer

Statistical mediation analyses provide tools to disentangle and assess the relative magnitude of different causal pathways and mechanisms by which a predictor (or exposure) may affect an outcome. The basic concepts of mediation analysis sound simple – but this is deceptive. Commonly occurring scenarios such as confounding, effect modification, categorical or time-to-event outcomes, and multiple mediators introduce the potential for biased results and/or pitfalls. Only over the last decade, new methods have been developed to resolve many of these problems satisfactorily. This was done by interpreting the problem of mediation in the framework of potential outcomes ('counterfactuals') and applying concepts of causal inference.

A common approach to assess causal pathways through multiple mediators individually is sequential mediation analysis, i.e. the sequential assessment of the joint contribution of various sets of mediators, and then evaluating the resulting differences. However, this approach is inappropriate as soon as unmeasured confounding among the mediators is thought to be present. Vansteelandt and Daniel have recently (2017) presented a theoretical framework under which a valid effect decomposition into so-called interventional effect is possible even in this case, also proposing methods for estimation of these effects.

An example of a strongly interrelated set of variables where the sequential mediation analysis approach fails, is the cluster of phenotypes making up the metabolic syndrome. Such metabolic factors, specifically insulin resistance (as a precursor of diabetes), hypertension, hyperuricemia, and hypercholesterolemia, are also hypothesized to lie in the causal pathway linking obesity with increased risk of end-stage kidney disease. However, the exact contribution of these various pathways has not been investigated in large cohort data to date. Using the Vorarlberg Health Monitoring and Promotion Program (VHM&PP) database linked to the Austrian Dialysis and Transplant Registry (OEDTR) and the National Mortality Registry, we investigated this nephrological research question using the Vansteelandt&Daniel approach. We show that the effect of BMI on risk of end-stage kidney disease is completely mediated by the set of all four mediators, and that the contribution of hypercholesterolemia is negligible.

Subject-specific Networks as Predictive Features for Prognostic Modelling - A Scoping Review

Mariella Gregorich, Georg Heinze

The issue of how predictors should be incorporated into prognostic models still persists and needs to evolve with the ever-increasing availability of high-throughput technologies able to measure gene-expression and other omics data at an unprecedented level of detail. More and more researchers progressively reinforce the idea of patterns of connections across biological components being relevant for disease manifestation or prognosis rather than single biomarkers. Therefore, quantities that capture the system behaviour of interacting explanatory features could enhance approaches to prognosis. Network-derived attributes summarize important aspects of these interconnected systems and can add prognostic value not captured by the separate inclusion of variables. In order to identify current

subject-specific network approaches in use in medical application, we conducted a scoping literature review identifying articles that aim at the inclusion of subject-specific networks and/or graph-theoretical attributes of subject-specific networks as predictors in prognostic modelling.

A hierarchical clustering and data fusion approach for disease subtype discovery

Bastian Pfeifer, Michael Schimek

Recent advances in multi-omics clustering methods enable a more fine-tuned separation of cancer patients into clinical relevant clusters. These advancements have the potential to provide a deeper understanding of cancer progression and may facilitate the treatment of cancer patients.

We have developed a hierarchical clustering and data fusion approach, named HC-fused, for the detection of disease subtypes. Unlike other methods, the proposed approach naturally reports on the individual contribution of each single-omic to the data fusion process. Multi-view simulations with disjoint and disjunct cluster elements across the views indicate fundamentally different data integration behaviour of various state-of-the-art methods. HC-fused combines the strengths of some recently published methods and shows superior performance on real world cancer data from the TCGA (The Cancer Genome Atlas) database. Its overall conceptual simplicity fosters the interpretability of the final results, which is an important need in biomedical applications.

Evaluating selective inference for the Lasso: a comparative simulation study and practical considerations

Michael Kammer, Daniela Dunkler, Stefan Michiels, Georg Heinze

Nowadays clinical predictive or diagnostic models are ubiquitous, facilitating personalized medicine and guiding therapy decisions. Developing such models often requires the use of variable selection or shrinkage techniques. However, classical methods for statistical inference to estimate e.g. confidence intervals are not applicable in such settings, as valid post-selection inference must account for the selection of the variables. One way to facilitate this is by means of the selective inference framework, which is concerned with providing valid inference when the statistical hypotheses to be tested are explored, and the corresponding answers are analysed using the same set of data. In recent years the methodology was developed for the widely used Lasso method, i.e. L1-penalized regression, but there are also approaches agnostic of the model selection procedure.

We present our experiences in working with the proposed selective inference framework. In a systematic simulation study in linear regression, including settings based on real clinical data, we applied techniques for selective inference to obtain confidence intervals for Lasso regression models and studied their properties such as selective coverage, power to exclude zero and stability. To discuss the practical applicability of selective inference we provide a real-data example using the freely available Johnson's body fat dataset, which is concerned with the estimation of body fat in men using correlated anthropometric body measurements.

We found available software for selective inference to be challenging to work with. Lasso confidence intervals tended to be very wide and quite variable, but could potentially improve model selection properties, in particular false positive findings. Selection agnostic methods, which are so far only available in linear regression, were found to be much more conservative and computationally more demanding,

limiting their practical usability. In conclusion, selective inference using the Lasso remains a challenging problem in practice as development of corresponding user-friendly software is still in its infancy.

Session 2

Risk prediction with discrete ordinal outcomes; calibration and the impact of the proportional odds assumption

Michael Edlinger, Maarten van Smeden, Hannes F Alber, Ewout W Steyerberg, Ben Van Calster

When evaluating the performance of risk prediction models, calibration is often underappreciated. There is little research on calibration for discrete ordinal outcomes.

We aimed to compare calibration measures for risk models that predict a discrete ordinal outcome (typically 3 to 6 categories), investigate the impact of assuming proportional odds on risk estimates and calibration, and study the impact of assuming proportional odds.

We studied multinomial logistic, cumulative logit, adjacent category logit, continuation ratio logit, and stereotype logistic models. To assess calibration, we investigated calibration intercepts and slopes for every outcome level, for every dichotomised version of the outcome, and for every linear predictor (i.e. algorithm-specific calibration). Finally, we used the estimated calibration index as a single-number metric, and constructed calibration plots.

We used large sample simulations to study the behaviour of the logistic models in terms of risk estimates, and small sample simulations to study overfitting. As a case study, we used data from 4,888 symptomatic patients to predict the degree of coronary artery disease (five levels, from no disease to three-vessel disease).

Models assuming proportional odds easily resulted in incorrect risk estimates. Calibration slopes for specific outcome levels or for dichotomised outcomes often deviated from unity, even on the development data. Non-proportional odds models, however, suffered more from overfitting, because these models require more parameters. Algorithm-specific calibration for proportional odds models assumes that this assumption holds, and therefore did not fully evaluate calibration.

Deviations from the proportional odds assumption can result in poor risk estimates and calibration. Therefore, non-proportional odds models are generally recommended for risk prediction, although larger sample sizes are needed.

How to maximize and minimize response rates in online surveys

Alexander Avian

Coronavirus disease 2019 (COVID-19) represents a significant challenge to health care systems around the world. A well-functioning primary care system is crucial in epidemic situations as it plays an important role in the development of a system-wide response. 2,678 Australian, Austrian, German and Italian general practitioners (GPs) answered an online baseline questionnaire regarding their experiences during the first wave of the COVID-pandemic. Afterwards they were invited to answer several follow up surveys (up to eight follow up surveys). Country specific different strategies were followed to invite and motivate GPs to

take part in the follow up surveys. While in Australia response rate decreased to 0% in the last follow up, in Austria/Germany and Italy response rates only decreased to 30%. Using special strategies can increase response rates even in studies including many follow-ups.

Testing procedures for the comparison of multiple characteristics of different survival functions

Robin Ristl

Survial and other time-to-event variables are widely used endpoints in clinical trials. In a typical clincial trial comparing a treatment and a control group with respect to a time-to-event outcome, confirmatory inference and quantification of the treatment effect is based on the hazard ratio estimated from a proportional hazards model. In absence of the proportional hazards assumption, the usual hazard ratio estimate is not a reliable measure of treatment effect, though, because it depends on the censoring pattern, the study duration and the recruitment regimen in combination with the actual survival distribution. In cases of crossing hazard functions or crossing survival functions the use of the hazard ratio as effect measure is further reduced.

In these settings it may be more appropriate to quantify the difference in survival functions by a set of more than one, well interpretable, parameters. Such parameters may be the difference in predefined x-year survival probabilities, e.g. in 1-year and 2-year survival, the difference in quantiles of the survival functions, e.g. difference in medians, and an average hazard ratio up to a preset time-point.

Whenever more than one parameter is considered to assess the treatment effect in a confirmatory way, an inference approach with control of the family wise type I error rate and predefined simultaneous coverage of confidence intervals is warranted. By applying the counting process representation of survival function estimates, we show that the proposed estimates are asymptotically multivariate normal and we derive an estimate of their asymptotic covariance matrix and normality-based simultaneous confidence intervals. As an alternative method for constructing simultaneous confidence intervals we apply the perturbation approach for survival function estimates, which is similar to a parametric bootstrap.

The finite sample properties of the proposed methods are investigated in a simulation study showing coverage probabilities close to the nominal value even for moderate sample sizes.

Designing and simulating exploratory platform trials

Elias Meyer

In the last months and years - further fueled by the global COVID-19 outbreak - master protocol trials and especially platform trials have received great attention and are nearly unanimously considered to hold great potential for future drug development. We firstly present the results of a systematic literature review on master protocol trials, focusing on definitions and actually planned and conducted trials. In a next step, we investigate available software to simulate platform trials and share key findings regarding essential features such a software must offer. Finally, we present the results of a simulation study on an open-entry, cohort platform trial design comparing combination therapies to the respective monotherapies and standard-of-care and provide some outlook on an upcoming R package for platform trial simulation.