Eurocim 2024 – Poster presentations

Day: Wednesday, Board 1, Side A

Title: Manipulating a Continuous Instrumental Variable: Algorithm, Partial Identification Bounds, and Inference under Randomization and Biased Randomization Assumptions

Presenter: Zhe Chen

Affiliation: University of Illinois Urbana-Champaign

Coauthors: Min Haeng Cho, Bo Zhang

Abstract: An instrumental variable (IV) can be thought of as a random encouragement towards accepting a treatment. With a continuous IV, Baiocchi et al. (2010) propose to 'strengthen' the original IV using a design technique called 'non-bipartite matching.' Their key insight is to shift focus to a possibly smaller cohort amenable to being paired with a larger separation in the IV dose, thus inducing a higher compliance rate. Three elements change as one switches between IV-based designs. First, the study cohort changes. In this work, we show this can be avoided using a non-bipartite, template matching algorithm. Second, the compliance rate changes. Third, the latent complier subgroup changes as a person's principal stratum is defined with respect to the two IV doses within each pair. This third element is important because the effect ratio estimand concerns the treatment effect among compliers, so the causal estimand is dictated by the design. In this work, we study partial identification bounds for the sample average treatment effect (SATE) in a IV-based matched cohort study. Unlike effect ratio, the SATE estimand does not depend on who is matched to whom in the design, although a strengthened-IV design has the potential to narrow its partial identification bounds. We derive valid inference for the partial identification bounds under a randomization assumption and an IV-dose-dependent, biased randomization scheme in a matched-pair design. We apply the proposed study design and methods to a study of the effect of neonatal intensive care units on the mortality rate of premature babies.

Day: Wednesday, Board 1, Side B

Title: The impact of job stability on monetary poverty in Italy: causal small area estimation

Presenter: Katarzyna Reluga

Affiliation: University of Bristol

Coauthors: Dehan Kong, Setareh Ranjbar, Nicola Salvati, Mark van der Laan

Abstract: Job stability refers to the security and predictability of employment, including factors such as long-term contracts, adequate wages, social security benefits, and access to training and career development opportunities. Stable employment can play a crucial role in reducing poverty, as it provides individuals and households with a stable income as well as improves their overall and subjective economic well-being. In this work, we leverage the EU-SILC survey and census data to assess the causal effect of job stability on monetary poverty across provinces in Italy. To this end, we propose a causal small area estimation (CSAE) framework for heterogeneous treatment effect estimation in which only a negligible fraction of outcomes is observed at the provincial level. Our estimators are more stable than the classical causal inference tools as they borrow strength from the other sources of data at the expense of additional modelling assumptions. On top of that, our new methodology proves to be successful in recovering provincial heterogeneity of the effect of job stability across six regions in Italy.

Day: Wednesday, Board 2, Side A

Title: Cumulative incidence estimation with external controls in competing risk analysis

Presenter: Zehao Su

Affiliation: University of copenhagen

Coauthors: Frank Eriksson

Abstract: Recent years has seen a surge in the interest for augmenting the control arm in clinical trials with external data to boost the statistical power. While some groundwork has been laid for data fusion methods for time-to-event outcomes, there is a lack of literature on competing risk analysis. To formulate an appropriate transportability assumption, we revisit hazard as an interpretable object in multi-state models. Under the transportability on the hazard of the event of interest on the control treatment, we derive the semiparametric efficiency bounds for causal cumulative incidences. Additionally, we propose doubly-robust estimators that can achieve these bounds asymptotically. The efficiency gain from incorporating the external controls is demonstrated both theoretically and with numerical studies. Furthermore,

we discuss other transportability assumptions which are connected to particular causal effects in competing risk analysis.

Day: Wednesday, Board 2, Side B

Title: A latent causal inference framework for ordinal variables

Presenter: Martina Scauda

Affiliation: University of Basel, Dep. of Mathematics and Computer Science, Switzerland and University of Cambridge, Statistical Laboratory, UK

Coauthors: Jack Kuipers (ETH Zurich, Dep. of Biosystems Science and Engineering, Switzerland), Giusi Moffa (University of Basel, Dep. of Mathematics and Computer Science, Switzerland and University College London, Division of Psychiatry, UK)

Abstract: Ordinal data, including Likert scales, economic status, and education levels are commonly encountered in applied research. Yet, existing causal methods often fail to account for the inherent order among categories, as they are primarily developed either for nominal data or for continuous data where relative magnitudes are well-defined. Hence, there is a pressing need for an order-preserving methodology to compute interventional effects between ordinal variables. Presuming a latent Gaussian Directed Acyclic Graph (DAG) model as data-generating mechanism provides one possible solution. Precisely, the model assumes that ordinal variables originate from marginally discretizing at given thresholds a set of Gaussian variables, whose latent covariance matrix is constrained to satisfy the conditional independencies inherent in a DAG. Conditionally on a given latent covariance matrix and thresholds, this model leads to a closed-form function for ordinal causal effects in terms of interventional distributions in the latent space. For binary variables, this approach reduces to classical methods for causal effect estimation. When the underlying DAG is unknown, one can use the Ordinal Structural EM (OSEM) algorithm to learn both a plausible latent DAG, up to an equivalence class, and the model's parameters from observational data. Simulations demonstrate the performance of the proposed approach in estimating ordinal causal effects both for known and unknown structures of the latent graph. As an illustration of a real-world use case, the method is applied to survey data of 408 patients from a study on the functional relationships between symptoms of obsessive-compulsive disorder and depression.

Day: Wednesday, Board 3, Side A

Title: Distinguishing the effects of prenatal exposure to surgery and anesthesia on development of ADHD using a separable effects model

Presenter: Caleb Miles

Affiliation: Columbia University

Coauthors: Amy Pitts, Caleb Ing, Ling Guo

Abstract: The U.S. Food and Drug Administration has cautioned that prenatal exposure to anesthetic drugs during the third trimester may have neurotoxic effects; however, there is limited clinical evidence available to substantiate this recommendation. To explore this claim, we analyze data from the nationwide Medicaid Analytic eXtract (MAX) from 1999 through 2013, which linked 16,778,281 deliveries to mothers enrolled in Medicaid during pregnancy. The aim of our analysis is to estimate the causal effect of exposure to anesthesia in utero on the diagnosis of attention-deficit/hyperactivity disorder (ADHD) in the child. Isolating the effect of anesthesia from the effect of the surgical procedure is challenging due to these exposures being deterministically linked, thereby inducing an extreme positivity violation. To overcome this, we adopt the separable effects framework of Robins and Richardson (2010) to isolate the effect of anesthesia by blocking effects through variables that are assumed to completely mediate the causal pathway from surgery to ADHD. Furthermore, we develop sensitivity analyses to assess the impact of violations to our key identifying assumptions.

Day: Wednesday, Board 3, Side B

Title: AggregATEs

Presenter: Giacomo Opocher

Affiliation: University of Bologna

Abstract: The regression discontinuity (RD) design is one of the most widely used non-experimental methods for causal inference. At the cost of bounding the heterogeneity of treatment effects, I propose a method that identifies the same individual-level parameter, relying solely on aggregate-level data. In the presence of a change in the RD cutoff, I exploit the share of individuals who become eligible as a source of exogenous variation of the change in the share of treated to identify its impact on the change in the outcome. This exercise provides a consistent estimator for the individual-level average treatment effect. Without a real change in the cutoff, researchers can consider a fictitious one and derive a similar estimator, with the same properties. I discuss the potential problems that arise in the presence of heterogeneous treatment effects.

Day: Wednesday, Board 4, Side A

Title: When to switch from controlled to assisted ventilation mode in mechanically ventilated patients. A target trial emulation.

Presenter: Carmen Reep

Affiliation: Erasmus MC, Rotterdam, the Netherlands

Coauthors: Lucas Fleuren, Evert-Jan Wils, Leo Heunks

Abstract: In mechanically ventilated intensive care patients, switching from a controlled to an assisted ventilation mode is a critical first step in weaning patients from the ventilator. Switching too early may induce lung injury and respiratory distress, while switching too late increases the risk of ventilator-associated complications. Since there are currently no guidelines on when to switch, we first examined the effect of early or late switching and secondly the optimal arterial partial pressure to fraction of inspired oxygen ratio (P/F ratio) on successful extubation. We set up a target trail emulation using the prospective and multicentre WEAN-SAFE dataset. Patients were eligible if they were on controlled mechanical ventilation for two calendar days and had a P/F ratio >150. We examined an early switch (grace period of 1 day) to an assisted mode versus a late switch (after 1 day). Secondly, we compared the effect of switching above a P/F ratio of 150, 200 or 250. We used a clone-censor-weight design, with weights obtained using pooled-logistic-regressions models. Our outcome was the cumulative incidence of successful extubation at 30 days, accounting for competing event 'death' using a weighted Aalen-Johansen estimator. We included 1257 patients. Early switching showed a 13% [5 – 22%] higher cumulative incidence of successful extubation than late switching. Switching when P/F>150 showed a 12% [2 – 23%] improvement over a P/F>200 and a 15% [4 – 27] improvement over P/F>250. This target trial emulation shows that an early switch at a P/F ratio above 150 leads to earlier and more successful extubations.

Day: Wednesday, Board 4, Side B

Title: Constructing Synthetic Treatment Groups without the Mean Exchangeability Assumption

Presenter: Yuhang Zhang

Affiliation: Peking University

Coauthors: Yue Liu and Zhihua Zhang

Abstract: The purpose of this work is to transport the information from multiple randomized controlled trials to the target population where we only have the control group data. Previous works rely critically on the mean exchangeability assumption. However, as pointed out by many current studies, the mean exchangeability assumption might be violated. Motivated by the synthetic control method, we construct a synthetic treatment group for the target population by a weighted mixture of treatment groups of source populations. We estimate the weights by minimizing the conditional maximum mean discrepancy between the weighted control groups of source populations and the target population. We establish the asymptotic normality of the

synthetic treatment group estimator based on the sieve semiparametric theory. Our method can serve as a novel complementary approach when the mean exchangeability assumption is violated. Experiments are conducted on synthetic and real-world datasets to demonstrate the effectiveness of our methods.

Day: Wednesday, Board 5, Side A

Title: Estimation of causal treatment effects in cross-over trials

Presenter: Christian Pipper

Affiliation: Novo Nordisk

Coauthors: Thomas Scheike; Jeppe Madsen

Abstract: We introduce causal inference reasoning to cross-over trials, with a focus on Thorough QT (TQT) studies. For such trials, we propose different sets of assumptions and consider their impact on the modelling strategy and estimation procedure. We show that unbiased estimates of a causal treatment effect are obtained by a g-computation approach in combination with weighted least squares predictions from a working regression model. Only a few natural requirements on the working regression and weighting matrix are needed for the result to hold. It follows that a large class of Gaussian linear mixed working models lead to unbiased estimates of a causal treatment effect, even if they do not capture the true data generating mechanism. We compare a range of working regression models in a simulation study where data are simulated from a complex data generating mechanism with input parameters estimated on a real TQT data set. In this setting, we find that for all practical purposes working models adjusting for baseline QTc measurements have comparable performance. Specifically, this is observed for working models that are by default too simplistic to capture the true data generating mechanism. Cross-over trials and particularly TQT studies can be analysed efficiently using simple working regression models without biasing the estimates for the causal parameters of interest.

Day: Wednesday, Board 5, Side B

Title: Use of genetic correlations to examine selection bias

Presenter: Chin Yang Shapland

Affiliation: University of Bristol

Coauthors: Apostolos Gkatzionis, Gibran Hemani and Kate Tilling

Abstract: Observational studies are rarely representative of their target population, because there are known and unknown factors that affect an individual's choice to participate (known

as the selection mechanism). Selection can cause bias in a given analysis, if the outcome is related to selection (conditional on the other variables in the model). However, the selection mechanism usually cannot be detected from the observed data if we have no data on the non-selected sample - for example, when the selected sample is participants in a research study. Here, we develop methods to examine the selection mechanism by comparing correlations among variables in the selected sample to those expected under no selection. We examine the use of four hypothesis tests to identify induced associations between genetic variants in the selected sample. We evaluate these approaches with Monte Carlo simulations. Finally, these approaches are demonstrated with an applied example, using data from UK Biobank (UKBB), with alcohol intake as exposure to test the presence of selection bias. The proposed tests have identified selection due to alcohol intake into UKBB, and the subsample of individuals with weekly alcohol intake. Analyses in UKBB with alcohol consumption as exposure or outcome may be biased by this selection.

Day: Wednesday, Board 6, Side A

Title: Treatment regime spillover: Estimating the causal effect of treatment regimes in resource constrained settings

Presenter: David Vock

Affiliation: University of Minneosta

Abstract: A dynamic treatment regime (DTR) is clinical decision tool which dictates what treatment a patient should receive based on evolving patient characteristics. Existing methods can estimate the effect of DTRs on survival outcomes, but these were developed for applications where treatment is abundantly available. In a context when treatment is limited (e.g., deceased donor organs, CAR T-Cell therapies, etc.), the availability and type of treatment will vary depending on the rules other patients use to accept or decline offered treatment and the order or process by which treatment is offered to potential recipients (i.e., the allocation rules). Therefore, when (or if) a patient receives treatment while following regime g is random and depends on the regimes other patients use to accept or decline treatment. We refer to this as "regime spillover." To estimate the anticipated survival if a random individual were to adopt a DTR g under different counterfactual regimes other patients use to accept or decline treatment, we develop a novel inverse probability weighted estimator (IPCW) which re-weights patients based on the probability of following their treatment history in that counterfactual world. We estimate this counterfactual probability using hot deck imputation to fill in data that is not observed for patients who are artificially censored by IPCW once they no longer follow the DTR of interest. We show via simulation that our proposed methods have good finite-sample properties, and we apply our method to a lung transplantation observational registry.

Day: Wednesday, Board 6, Side B

Title: Evidence triangulation for causal loop diagrams: constructing biopsychosocial models using group model building, literature review, and causal discovery

Presenter: Jeroen Uleman

Affiliation: University of Copenhagen

Abstract: The complex nature of many urgent public health problems necessitates systems thinking tools like causal loop diagrams (CLDs) to visualize the underlying causal network and enable computational simulations of potential interventions. However, the information necessary to construct these diagrams is limited within any single data source and reflects source-specific biases. For this reason, the present study utilizes a mixed-methods evidence triangulation approach to construct CLDs, which integrates information from three sources: 1) a group of domain experts, 2) scientific literature, and 3) numerical data from empirical studies.We present a case study on the onset of depressive symptoms in response to daily stressors in healthy adults, considering biological, psychological, behavioral, and social dimensions. The evidence triangulation process combines theory- and expert-based group model building and literature review with data-driven causal discovery. Our findings indicate that the triangulation of evidence impacts the CLD in three ways. First, modifications to the causal structure resulted in greater comprehensiveness, adding links that could have otherwise been missed. Second, changes to the feedback loops suggest altered dynamics, affecting how the different variables change together over time. Third, more transparency regarding available evidence provides a measure of uncertainty, indicating opportunities for future research. These findings suggest that evidence triangulation can result in higher-quality CLDs, indicating an important potential in advancing our understanding of complex public health problems.

Day: Wednesday, Board 7, Side A

Title: Assumption-Lean Quantile Regression

Presenter: Georgi Baklicharov

Affiliation: Ghent University

Coauthors: Stijn Vansteelandt, Christophe Ley

Abstract: Quantile regression is a powerful tool for detecting exposure-outcome associations given covariates across different parts of the outcome's distribution, but has two major limitations when the aim is to infer the effect of an exposure. Firstly, the exposure coefficient estimator may not converge to a meaningful quantity when the model is misspecified, and secondly, variable selection methods may induce bias and excess uncertainty, rendering inferences biased and overly optimistic. In this paper, we address these issues via partially linear

quantile regression models which parametrize the conditional association of interest, but do not restrict the association with other covariates in the model. We propose consistent estimators for the unknown model parameter by mapping it onto a nonparametric main effect estimand that captures the (conditional) association of interest, even when the quantile model is misspecified. This estimand is estimated using the efficient influence function under the nonparametric model, allowing for the incorporation of data-adaptive procedures such as variable selection and machine learning. Our approach provides a flexible and reliable method for detecting associations that is robust to model misspecification and excess uncertainty induced by variable selection methods.

Day: Wednesday, Board 7, Side B

Title: Sparsity-inducing BART+SPL for population average treatment effect estimation with high-dimensional covariates

Presenter: Lennard Maßmann

Affiliation: University of Duisburg-Essen

Abstract: The ability to draw causal inferences from observational data in the potential outcome framework relies on the positivity assumption. However, many real-world datasets suffer from non-overlap regions leading to a decisive violation of the positivity assumption. To solve this issue, methods like trimming or weighting are commonly used. These methods have limitations due to specific modeling assumptions and changes to the underlying population being considered. To overcome these challenges, the Bayesian modeling approach BART+SPL has been developed. It combines Bayesian Additive Regression Trees (BART) and a spline model (SPL) to adaptively discriminate between overlap and non-overlap regions. This method can estimate the population average treatment effects with lower model dependence and provides suitable uncertainty quantification even in the non-overlap region. However, when analyzing high-dimensional covariates, the performance of BART+SPL deteriorates, leading to bias and severe undercoverage when irrelevant covariates increase. To address this issue, this paper proposes an extension of BART+SPL that adapts to sparsity by using Dirichlet Additive Regression Trees and soft decision rules in the imputation phase of the algorithm. In addition, the spline model no longer relies on an unidentifiable variance inflation parameter to account for higher uncertainty in regions of non-overlap, as introduced in the original BART+SPL algorithm. Simulation studies show that the proposed sparsity-inducing BART+SPL algorithm improves precision and coverage when estimating population average treatment effects with high-dimensional covariates and overlap violations, compared to the original BART+SPL algorithm.

Day: Wednesday, Board 8, Side A

Title: Data-Adaptive Interventions for Causal Inference under Positivity Violations

Presenter: Han Bao

Affiliation: University of Munich

Coauthors: Michael Schomaker

Abstract: Positivity violations present persistent challenges in estimating causal effects, particularly for continuous interventions. While positivity violations have been addressed for binary interventions, the literature on continuous interventions remains underdeveloped, with a lack of comprehensive definitions, identification, and solutions. Existing research adjusts the estimand into a weighted version by projection functions or changes the research question via modified treatment policies, often compromising on interpretability or applicability. In contrast, we develop a theoretically robust and practically viable framework for the identification of positivity violations, coupled with the formulation of a data-adaptive intervention strategy that effectively mitigates such issues.We define the data-adaptive interventions based on the intervention of interest, which is applied when its conditional density given the covariates exceeds a critical threshold according to the high-density regions. Otherwise, a substitute intervention is determined data-adaptively to be situated within high-density regions yet optimally balance some practicality. For instance, we prioritize feasibility, which is defined as maintaining a minimum distance from the intervention of interest. Simulation studies designed to replicate several scenarios of continuous interventions demonstrate a reduction in bias with our newly proposed method, notably in cases where the outcome model is misspecified and the intervention of interest has low density.Our method provides a promising solution for addressing positivity violations for continuous interventions. Under correct specification of the treatment regime, it effectively reduces the bias and improves the stability of estimation. The estimand is straightforward and interpretable, offering advantages over weighted estimand, and is closely aligned with general research questions.

Day: Wednesday, Board 8, Side B

Title: A Markov property for sample paths of stochastic processes

Presenter: Philip Boeken

Affiliation: University of Amsterdam

Coauthors: Joris M. Mooij

Abstract: We prove a graphical Markov property for sample paths of various discrete- and continuous-time stochastic processes. When a dynamical system is modelled by a set of (ordinary, partial, or stochastic) differential equations, the existence and uniqueness of solutions

can yield the existence of a (deterministic) solution function, that takes initial conditions and sample paths of exogenous noise processes as input, and maps them to the sample path of the solution of the differential equation. Similarly, sample paths of variables of a dynamic Bayesian Network can be expressed as measurable (deterministic) functions of sample paths of other variables, and an exogenous noise process.This approach allows to model the sample paths of various stochastic processes with SCMs, where the variables are entire sample paths of the process, and the structural equations are the measurable solution functions as described above. For the graph of this SCM, existing work by Forré, Mooij and Bongers yields a Markov property. This provides a 'global' alternative to the local independence graph as developed by Didelez, Mogensen and Hansen. Our Markov property implies a do-calculus for interventions on the level of entire sample paths. Combined with recent developments in conditional independence testing for functional data, this might be a promising approach for 'global' causal discovery and reasoning for time series data.

Day: Wednesday, Board 9, Side A

Title: Explainability in Causal Discovery: A Novel Approach for Inferring Causal Graphs from Observational Data

Presenter: Jesus Renero

Affiliation: Industry Doctoral Student UNAV

Coauthors: Idoia Ochoa, Roberto Maestre

Abstract: Causal discovery is a critical task in various fields, including medicine, economics, and social sciences, aiming to infer causal relationships from observational data. However, the existing methods often yield highly variable results, requiring manual tuning or leading to indistinguishable Markov equivalent classes. In this work, we propose a novel approach, Regression-EXplainability-based causal discovery (REX), which leverages machine learning explainability techniques to support the causal graph building process under the causal sufficiency and faithfulness assumptions. Our experiments demonstrate that REX consistently detects cause-effect drivers in synthetic continuous data, yielding DAGs aligning with the true underlying relationships. We also introduce the REX method, which utilizes Shapley values and independence tests to infer causal graphs from observational data. Our findings reveal a strong correlation between Shapley values, conditional independence of variables, and causal edges, supporting the use of Shapley values as a proxy to infer the causal graph. Furthermore, our method, particularly one of the REX variants, exhibits balanced performance and relative robustness against missing true causal links, highlighting its utility in complex causal discovery tasks. Code and datasets will be made available in a GitHub repository upon acceptance. This study is under ongoing research, focusing on further enhancing the method and exploring its applicability to real-world datasets, with the ultimate goal of advancing the state of the art in causal inference.

Day: Wednesday, Board 9, Side B

Title: Identification of interventional effects in stochastic differential equation systems from cross-sectional data

Presenter: Cecilie Olesen Recke

Affiliation: University of Copenhagen

Coauthors: Jeffrey Adams and Niels Richard Hansen

Abstract: We study causality in systems that allow for feedback loops among the variables via models of cross-sectional data from a dynamical system. Specifically, we consider operator self-decomposable (OSD) distributions, which appear as steady-state distributions for a class of Markov processes that solve a stochastic differential equation (SDE). This allows us to define interventions in the system, and a main question is if the interventional distribution is identified from the observational distribution.We find a condition we call drift-volatility balance (DVB), which allows us to identify the interventional mean and variance from observational quantities. To test the DVB condition we first show that in the non-Gaussian case and under DVB we have generic identifiability of both the drift and volatility matrix. The result uses the Lyapunov equation of the third order cumulant. Using this we propose a goodness-of-fit test of DVB by testing the rank of a certain matrix depending on the third order cumulants and the precision.

Day: Wednesday, Board 10, Side A

Title: The Cheap Subsampling Bootstrap for Longitudinal Causal Inference

Presenter: Johan Sebastian Ohlendorff

Affiliation: University of Copenhagen, Section of Biostatistics

Abstract: Numerous methods for estimating longitudinal effects have been proposed for the intervention-specific meanoutcome. However, a common limitation is that a variance estimator may not be readily available or reliable(due to e.g., positivity violations). In such cases, bootstrapping can be a valuable alternative. Still, theestimation of rather simple target parameters, such as the intervention-specific mean outcome can be verytime-consuming due to the use of machine learning models in the estimation of the nuisance parameters. Thisissue may render bootstrapping practically unfeasible.In this presentation, we consider the Cheap Subsampling confidence interval which is a modification of Lam(2022). This confidence interval is based on recalculating estimates on B 1 subsamples of size m < nand has a coverage that converges to the nominal level of 1 − for any number of resamples B 1 andsubsample size m with m/n → 0 as m, n → ∞. This is different from typical confidence intervals based onbootstrapping since these require a larger number of resamples to be asymptotically

valid. Thus confidenceintervals can be constructed at a low computational cost. An additional advantage is that subsamplingincreases the applicability for learners utilizing internal cross-validation. However, we still need to choose anappropriate number of resamples since the Cheap Subsampling confidence intervals may vary significantly fora low number of resamples and the subsample size m. We address these issues in a simulation study.

Day: Wednesday, Board 10, Side B

Title: Safety of vaginal estrogen therapy after early-stage breast cancer: a nationwide population-based target trial emulation.

Presenter: Elise Dumas

Affiliation: Ecole polytechnique Fédérale de Lausanne (EPFL)

Coauthors: Anne-Sophie Hamy, Paul Gougis, Enora Laas, Sophie El Ferjaoui, Floriane Jochum, Diane Hill, Christine Rousset-Jablonski, Kerollos Nashat Wanis, Philippe-Jean Bousquet, Sophie Houzard, Christine Le Bihan-Benjamin, Fabien Reyal, Mats Julius Stensrud, Florence Coussy

Abstract: Breast cancer (BC) survivors frequently experience genitourinary symptoms due to declining estrogen levels. While vaginal estrogen therapies (VETs), such as estriol and promestriene, are known to alleviate these symptoms, their impact on BC prognosis remains uncertain, and may vary depending on the tumor's hormonal receptor (HR) status and the endocrine therapy regimen. Using nationwide French health insurance claims data, we emulated a target trial assessing the effect of VET (any molecule, promestriene, or estriol) initiation on disease-free survival (DFS) in BC survivors. We performed subgroup analyses based on HR status (HR-positive / HR-negative) and endocrine therapy regimen in patients with HR-positive tumors (aromatase inhibitor AI / tamoxifen). Of the 368,597 patient-years across 134,942 patients included in the analyses, 1,739 initiated VET. We found that VET initiation slightly decreased DFS in patients with HR-positive tumors (-2.1 percentage points at five years, 95% CI: -4.8 to 0.1), particularly in those treated with AIs (-3.0, 95% CI: -6.5 to -0.3). Conversely, no reduction in DFS was observed in HR-negative or tamoxifen-treated patients. In AI-treated patients, the initiation of estriol led to a more premature and severe decrease in DFS (-4.2 percentage points over three years, 95% CI: -8.7 to -0.1) compared to promestriene (1.0, 95% CI: -0.9 to 2.9). Our results suggest that the use of VET is safe in individuals with HR-negative tumors and in those concurrently treated with tamoxifen, but caution its use in AI-treated patients. For this subgroup, we recommend avoiding VET, or opting for promestriene over estriol.

Day: Wednesday, Board 11, Side A

Title: A general framework for Causal Learning algorithms

Presenter: Kai Teh

Affiliation: UCL

Coauthors: Kayvan Sadeghi, Terry Soo

Abstract: We present a general framework for constructing all exact causal learning algorithms, along with corresponding sufficient conditions for consistency. By appropriate substitution, our framework includes previous work in exact causal learning including conventional SGS, sparsest permutation algorithm, and more recent ones such as natural structure learning using ordered stabilities. We then apply the framework to obtain a relaxed version of the natural structure learning algorithms, along with sufficient and necessary conditions for consistency. We then present the construction of such an algorithm, which we call (Me)-LoNS, and compare the conditions for consistency of our approach to some existing causal learning approaches

Day: Wednesday, Board 11, Side B

Title: Emulating trials using King's College Hospital's electronic health records

Presenter: Giulio Scola

Affiliation: King's College London

Coauthors: Dr. Jack Wu, Dr. Nilesh Pareek, and Prof. Sabine Landau.

Abstract: BackgroundThe target trial framework is used to estimate the causal effect of treatments using observational data. To assess the feasibility of using structured and unstructured data from the King's College Hospital's(KCH's) electronic health records(EHR) for trial emulations, we emulated a landmark heart failure(HF) trial – specifically, the Randomised Aldactone Evaluation Study(RALES). In a subsequent new trial emulation, we relaxed the eligibility criteria and extended the follow-up period from 2 to 5 years. MethodsThe RALES trial demonstrated that adding spironolactone to the standard treatment for severe HF reduced all-cause mortality. Leveraging KCH's EHR, we replicated the RALES trial and extended the follow-up period. We used Cox-proportional hazards and pooled logistic regression modelling to estimate the intention-to-treat effects of spironolactone on all-cause mortality at 2 years and 5 years, adjusting for baseline confounders using inverse-probability of treatment weighting. ResultsIn our RALES trial emulation study, of 139 eligible individuals there were 63 spironolactone initiators and 76 non-initiators. Both groups had similar characteristics in terms of age, potassium and creatinine concentrations. Over the 2-year follow-up, 29 individuals died. The estimated intention-to-treat hazard ratio at 2 years was 0.74 (95% confidence interval (CI):

0.33, 1.62). The estimated intention-to-treat hazard ratio at 5 years was 0.66 (95% CI: 0.44, 0.99).ConclusionsThe estimate from our RALES trial emulation falls within the 95% CI reported in the original RALES trial. This suggests the feasibility of estimating treatment effects using KCH's EHR and underscores the reliability of the results in our new trial emulation.

Day: Wednesday, Board 12, Side A

Title: Modeling Latent Selection with Structural Causal Models

Presenter: Leihao Chen

Affiliation: University of Amsterdam

Coauthors: Onno Zoeter, Joris Mooij

Abstract: Selection bias is ubiquitous in real-world data, and it can lead to misleading results if not dealt with properly. We introduce a conditioning operation on Structural Causal Models (SCMs) to model latent selection from a causal perspective. We demonstrate that the conditioning operation transforms an SCM with the presence of an explicit latent selection mechanism into a new SCM without explicit latent selection, encoding part of the causal semantics of the selected subpopulation according to the original SCM. Furthermore, we show that this conditioning operation preserves the simplicity, acyclicity, and linearity of SCMs, and it commutes with marginalization. In conjunction with marginalization and intervention, the conditioning operation offers a valuable tool for conducting causal reasoning tasks within causal models where latent details have been abstracted away.

Day: Wednesday, Board 12, Side B

Title: The target trial approach applied to causes of effects in addition to effects of interventions.

Presenter: Ian Shrier

Affiliation: Centre for Clinical Epidemiology, Lady Davis Institute, McGill University

Abstract: Some authors have proposed that epidemiology use an "interventionist" or "target trial" approach when analyzing observational studies. This forces investigators to define the population of interest, exposure comparisons, assignment procedures, follow-up period, and outcomes more precisely. However, others suggest the approach limits science to "effects of interventions" and ignores important causal questions related to "causes of effects". In this presentation, we generalize the interventionist approach to also answer these broader "causes of outcome" questions. We use the lens of Rothman's sufficient casual set framework, which considers causes to be states instead of actions. A well-defined intervention is simply one possible mechanism of changing a well-defined state to a different well-defined state. Considering

causes as states is consistent with the potential outcomes approach (with or without multi-state models), more recent work explaining well-defined interventions and counter-factuals in social epidemiology. In brief, the extension uses evidence synthesis across multiple "target trials" to answer "causes of effects" causal questions. "Effects of interventions" represent a special case where one can theoretically obtain an answer by "synthesizing evidence" over a single trial.

Day: Wednesday, Board 13, Side A

Title: Evaluating causal effects on time-to-event outcomes in an RCT in Oncology with treatment discontinuation

Presenter: Veronica Ballerini

Affiliation: University of Florence

Coauthors: Björn Bornkamp, Alessandra Mattei, Fabrizia Mealli, Craig Wang, Yufen Zhang

Abstract: In clinical trials, patients sometimes discontinue study treatments prematurely due to adverse events. Since treatment discontinuation occurs after the randomization as an intercurrent event, it makes causal inference more challenging. Although the Intention-To-Treat (ITT) analysis provides valid causal estimates of the effect of treatment assignment, it does not consider premature treatment discontinuation. To address this issue, we propose using principal stratification, a strategy recognized in the ICH E9 (R1) addendum for handling intercurrent events. Under this approach, we can decompose the overall ITT effect into principal causal effects for groups of patients defined by their potential discontinuation behavior in continuous time. However, this approach presents several complexities. Discontinuation in continuous time generates an infinite number of principal strata, and discontinuation time is not defined for patients who would never discontinue. Moreover, discontinuation time and time-to-event outcomes, often the primary endpoints in clinical trials, are subject to administrative censoring. To tackle these complexities, we employ a flexible model-based Bayesian approach, which provides easily interpretable results. We apply this Bayesian principal stratification framework to analyze synthetic data from an Oncology trial. Our aim is to assess the causal effects of a new investigational drug combined with standard of care versus standard of care alone on progression-free survival. We simulate data under different assumptions that reflect real scenarios where patients' behavior depends on critical baseline covariates. Finally, we highlight how this approach makes it straightforward to characterize patients' discontinuation behavior with respect to the available covariates with the help of a simulation study.

Day: Wednesday, Board 13, Side B

Title: Causal Modeling of Visual Fixations

Presenter: Jaime Maldonado

Affiliation: University of Bremen

Coauthors: Christoph Zetzsche and Vanessa Didelez

Abstract: When visually exploring the environment or images, the eyes move sequentially from one area of interest to the next. In natural viewing conditions, the eyes move up to 4 times per second without the person being fully aware of this. These movements are determined by visual cues (e.g., color and contrast) and cognitive processes (e.g., memory and attention). Visual fixations can be characterized by their duration, sequence, the low-level characteristics of the fixated areas (e.g., color and orientation), and the high-level content of the areas (e.g., a face or text). Understanding the mechanisms that drive this visual behavior has applications in cognitive neuroscience and applied fields such as advertisement, hardware and software interface design, and autonomous driving.Considering visual behavior as a causal problem, the image or scene can be formally regarded as the cause (i.e., the "treatment") and the eye movements as the effect. Additionally, the viewer's task (e.g., search for an object) can be regarded as an additional causal influence.A causal model of visual behavior could estimate the probability that a particular location is fixated and the duration of this fixation. Furthermore, the effect of high- and low-level factors and their influence on the sequence order can be determined. This work shows preliminary results of applying causal discovery in semantic and low-level annotations of images observed under free-viewing conditions. In this application, conducting randomized experiments would be impractical due to the ample combinatorial space of the variables; thus, causal discovery provides a practical exploratory tool.

Day: Wednesday, Board 14, Side A

Title: Fusing efficiency: A review of data fusion methods with PIONEER 6 case study

Presenter: Xi Lin

Affiliation: Department of Statistics, University of Oxford, UK

Coauthors: Jens Magelund Tarp, Robin J. Evans

Abstract: The integration of real-world data (RWD) and randomized controlled trials (RCTs) is becoming increasingly important in advancing causal inference in clinical research. This fusion holds great promise for enhancing the efficiency of average treatment effect estimation, thereby reducing the required number of trial participants and expediting drug access for patients in need. The FDA and EMA have recognized the complementary nature of these data

sources and their integration to improve the quality of evidence.Despite the multitude of available data fusion methods, choosing the most suitable one for a specific research question is challenging. This difficulty arises from the diverse assumptions, associated limitations, and implementation complexities.Our project aims to systematically review and compare data fusion methods, focusing on efficiency gain in average treatment effect (ATE) estimation. Through extensive simulations mirroring real-world scenarios, we identified a qualitative behaviour demonstrating a common risk-reward tradeoff across different methods. We investigate and interpret this tradeoff in various scenarios, providing important insights into understanding the strengths and weaknesses of different methods.This presentation offers a comprehensive overview of available methods, highlights key findings from simulation studies and presents a real-world case study where the PIONEER 6 trial is augmented with a US medical claims database for a more powerful ATE estimation.

Day: Wednesday, Board 14, Side B

Title: Bayesian Regression Discontinuity Design with Unknown Cutoff

Presenter: Julia Kowalska

Affiliation: Amsterdam University Medical Centers

Coauthors: Stéphanie van der Pas, Mark van de Wiel

Abstract: Regression discontinuity design (RDD) is a quasi-experimental approach used to estimate the causal effect of an intervention assigned based on a cutoff criterion. Regression discontinuity design exploits the idea that close to the cutoff units below and above are similar; hence, they can be meaningfully compared. Consequently, the causal effect can be estimated only locally at the cutoff point. This makes the cutoff point an essential element of the RDD. However, especially in medical applications, the exact cutoff location may not always be disclosed to the researcher, and even when it is, the actual location may deviate from the official one. Estimating the causal effect at an incorrect cutoff point leads to meaningless results, but since the cutoff criterion often acts as a guideline rather than as a strict rule, the location of the cutoff may be unclear from the data. We use a Bayesian approach to incorporate prior knowledge and uncertainty about the cutoff location in the causal effect estimation. At the same time, RDD is a local, boundary point estimation problem, whereas the Bayesian model is fitted globally to the whole data. In this work we address a natural question that arises: how to make Bayesian inference more local?

Day: Wednesday, Board 15, Side A

Title: Bayesian g-formula for causal mediation

Presenter: Alex Lewin

Affiliation: London School of Hygiene and Tropical Medicine

Coauthors: Jennifer Banks (LSHTM)

Abstract: Causal mediation methods are used to answer questions concerning mechanisms by which medical conditions or treatments have effects on later outcomes. The potential outcomes framework can be used to quantify direct and indirect effects between exposure/treatment, mediator and outcome. Implementing this counterfactual approach in the Bayesian framework is becoming more common. It retains the advantages of Bayesian statistics, such as the flexibility of dealing with missing data, a common problem when dealing with real world data, whilst allowing for causal conclusions to be drawn. However, the application of Robin's g-formula in this paradigm is relatively novel. This poster will present work in progress on a Bayesian g-formula for causal mediation. Continuous and binary longitudinal mediator covariates are considered. Markov-Chain Monte-Carlo iterative methods obtain posterior predictive distribution for parameter estimates, including causal parameters. On-going simulation work considers the validity of our approach across a range of scenarios. The approach will be applied to a study using UK electronic healthcare records to investigate mediators of the effect of atopic dermatitis and later heart failure. Finally, limitations using big data and potential biases will be considered and discussed.

Day: Wednesday, Board 15, Side B

Title: Causal Fair Machine Learning via Rank-Preserving Interventional Distributions

Presenter: Ludwig Bothmann

Affiliation: LMU Munich | Munich Center for Machine Learning (MCML)

Coauthors: Susanne Dandl, Michael Schomaker

Abstract: The machine learning (ML) community is increasingly aware of ethical issues surrounding automated decision-making (ADM) based on ML models. Fairness-aware ML is concerned with mitigating ML-related unfairness issues. Philosophically speaking, a decision can be defined as fair if equal individuals are treated equally and unequals unequally. Adopting this definition, the task of designing ML models that mitigate unfairness in ADM systems must include causal thinking when introducing protected attributes: Following our recent proposal, we define individuals as being normatively equal if they are equal in a fictitious, normatively desired (FiND) world, where the protected attributes have no (direct or indirect) causal effect on the target. We propose rank-preserving interventional distributions to define an estimand in this FiND world and a warping method for estimation. Evaluation criteria for both the success of the estimation method and the ML model, fitted in the warped world, are presented and validated through simulations. A data analysis showcases the practical application of our method and compares results with "fairadapt", an alternative approach for mitigating

unfairness by preprocessing data that uses quantile regression forests. With this, we show that our warping approach effectively identifies the most discriminated individuals and mitigates unfairness. This work contributes to the ongoing discourse on fairness in ML by incorporating causal thinking into the design of models for ADM systems – as increasingly used in health, economic and social sciences –, ensuring a more equitable treatment of individuals.

Day: Wednesday, Board 16, Side A

Title: A Generalized Parameterization for Mixed Data Linear Structural Equation Models

Presenter: Ankur Ankan

Affiliation: Radboud University

Coauthors: Johannes Textor

Abstract: Continuous variable Linear Structural Equation Models (SEMs) are parameterized using path coefficients, usually defined as the coefficients of a multiple regression model of each variable on its parents after scaling all variables to unit standard deviation. This parameterization allows for a straightforward interpretation of the strength of the relationship between the variables: a one-unit change in the cause variable, while keeping all other causes fixed, results in an expected change of the outcome variable that is equal to the path coefficient. Furthermore, path analysis can be applied to this parameterization to compute indirect and total effects between any two variables in the model easily. However, such regression-based parameterization is not available to mixed variable models, as categorical/ordinal variable regression, such as multinomial regression, produces a matrix of parameters, leading to a parameterization with no straightforward interpretation. Consequently, path analysis cannot be applied to such parameterization either.This talk presents preliminary work on a generalized parameterization for mixed data models, analogous to path coefficients in continuous variable models. We first show that the estimation of path ccoefficients for continuous variables can be reformulated in terms of the estimation of effect sizes between the residuals of the variables of interest, using their parents as covariates. We then show that we can extend this estimation approach to mixed variable models by combining a mixed data residualization method with a canonical correlation based effect size measure. This generalization gives us path coefficients like interpretable parametrization for mixed variable models.

Day: Wednesday, Board 16, Side B

Title: Antihypertensive target trial emulation using US electronic health records and weighting strategies to inform drug repurposing alternatives for dementia prevention

Presenter: Marie-Laure Charpignon

Affiliation: Massachusetts Institute of Technology, Broad Institute

Coauthors: Bella Vakulenko-Lagun, Colin Magdamo, Bowen Su, Sudeshna Das, Anthony Philippakis, Munther Dahleh, Deborah Blacker, Ioanna Tzoulaki, Mark Albers

Abstract: Alzheimer's disease, the most common type of dementia, affects 6.7 million Americans and costs $345B annually. Since disease-modifying therapies are limited, repurposing FDA-approved drugs may offer an alternative, expedited path to preventing dementia. Hypertension is a major risk factor for dementia onset. However, prior observational studies contrasting antihypertensive drug classes (Angiotensin Converting Enzyme inhibitors: ACEI, Angiotensin Receptor Blockers: ARB, and Calcium Channel Blockers: CCB), provided mixed results. We hypothesize that ACEI have an off-target pathogenic mechanism. To test this assumption, we emulate a target trial comparing patients initiating ACEI vs ARB using electronic health records from the US Research Patient Data Registry. We perform intention-to-treat analyses among patients aged 50+, applying Inverse Propensity score of Treatment Weighting to balance the two treatment arms and accounting for competing risk of death. In a cause-specific Cox Proportional Hazards (PH) model, the hazard of dementia onset was lower in ARB vs ACEI initiators (HR=0.72 [95% CI: 0.68-0.77]). Findings were robust to outcome model structures (i.e., Cox PH vs nonparametric) and generalized to patients with no hypertension diagnosis at initiation. Our trial emulation suggests that ARB initiation may reduce the risk of dementia onset. Future work will evaluate differential effects by brain penetrance and the mediating role of blood pressure control in dementia prevention.

Day: Wednesday, Board 17, Side A

Title: Causal inference for integrating external data in randomized trials

Presenter: Christiana Drake

Affiliation: University of California, Davis

Coauthors: Xiner Zhou

Abstract: Randomized trials often utilize a select group of study participants. This group does not typically represent the general population. After the randomized phase III study ends and the drug under investigation is found to have efficacy, an observational study follows to assess drug effectiveness in the general population. In chronic diseases with a placebo control group, if the drug is deemed effective, all subjects are switched to treatment. However, longterm effects of drug use are of interest. There is no longer a randomized control group and a comparison group must come from some other source. This type of study is no longer randomized and is an observational study subject to confounding. To minimize bias investigators often use historical control groups from similar studies of the same disease. The statistical techniques make use of the fact that one can compare before and after switch of experimental and control groups in the current trial as well as the before and after effects in the

external comparison group. We investigate and compare several approaches. The techniques are applied to a study of a novel drug treatment for Spinal Muscular Atrophy.

Day: Wednesday, Board 17, Side B

Title: Identifying Causal Effects of Nonbinary, Ordered Treatments using Multiple Instrumental Variables

Presenter: Nadja van 't Hoff

Affiliation: University of Southern Denmark

Abstract: This paper addresses the challenge of identifying causal effects of nonbinary, ordered treatments with multiple binary instruments. Next to presenting novel insights into the widely-applied two-stage least squares estimand, I show that a weighted average of local average treatment effects for combined complier populations is identified under the limited monotonicity assumption. This novel causal parameter has an intuitive interpretation, offering an appealing alternative to two-stage least squares. I employ recent advances in causal machine learning for estimation. I further demonstrate how causal forests can be used to detect local violations of the underlying limited monotonicity assumption. The methodology is applied to study the impact of community nurseries on child health outcomes.

Day: Wednesday, Board 18, Side A

Title: Identifiability of total effects from abstractions of time series causal graphs

Presenter: Emilie Devijver

Affiliation: CNRS - UGA

Coauthors: Charles Assaad, Eric Gaussier, Anouar Meynaoui, Gregor Gossler

Abstract: We study the problem of identifiability of the total effect of an intervention from observational time series only given an abstraction of the causal graph of the system. Specifically, we consider two types of abstractions: the extended summary causal graph which conflates all lagged causal relations but distinguishes between lagged and instantaneous relations; and the summary causal graph which does not give any indication about the lag between causal relations. We show that the total effect is always identifiable in extended summary causal graphs and we provide necessary and sufficient graphical conditions for identifiability in summary causal graphs.

Day: Wednesday, Board 18, Side B

Title: De-Biased Lasso for High-Dimensional Causal Inference

Presenter: Zewude Berkessa

Affiliation: University of Oulu, Research Unit of Mathematical Sciences

Coauthors: Patrik Waldmann

Abstract: Interference in the form of treatment versus control is one of the most straightforward causal experimental designs. However, many datasets are characterized by high dimensions, introducing complexities that can challenge traditional experimental designs. In observational data, adjusting for differences in observed features between treatment and control groups has recently attracted considerable interest, specifically in high-dimensional settings. To address this, approximate residual balancing (ARB) was proposed as a method to control high-dimensional confounders using a combination of l_1 and l_2 as a regularized regression adjustment in the potential outcomes framework for the estimation of treatment effects. This method imposes a penalty on the size of the regression coefficients, encouraging sparsity and reducing the number of confounders in the model. While the l_1-regularizer (lasso) is known for its convex nature and computational efficiency, it introduces a large estimation bias. Therefore, we propose a combination of l_1 and l_0 (best subset selection) to de-bias lasso as well as to tackle the computational infeasibility of l_0. Our new method is developed based on the proximal operator algorithm, which is built on the Peaceman-Rachford splitting method and proximal translation mapping. Currently, we are implementing our new method in the ARB framework. Evaluation on simulated data shows that our method, combined with Bayesian optimization of regularization parameters, achieves a lower variance estimation of the average treatment effects on the treated than the ARB method.

Day: Wednesday, Board 19, Side B

Title: Estimation of clinical utility in Emulated clinical trials

Presenter: Johannes Hruza

Affiliation: University of Copenhagen, Section of Epidemiology

Coauthors: Erin Gabriel, Michael Sachs, Arvid Sjölander

Abstract: Work in progress- In their 2020 paper, Sachs et al. outline how a prediction-driven decision rule needs to be evaluated not just for its predictive accuracy but for its clinical utility. Clinical utility can be summarized in several ways, but we will focus on the average outcome had the full population received treatment based on the proposed decision rule in comparison to the full population receiving the "standard" treatment assignment mechanism like physician's choice. Clinical trials to evaluate clinical utility are rarely conducted, and thus, Sachs et

al. propose an emulated clinical trials framework for observational data. However, only one simple estimator was suggested, and the particular details of estimation and identification were not discussed. We extend Sachs et al.'s work by considering several estimators of clinical utility. Clinical utility is an unusual estimand as one side of the contrast is always unconfounded, i.e. the standard of care is what is observed in the observation setting. We outline in detail the assumptions needed for identification of clinical utility and carefully consider positivity violations. In particular, we consider novel sigma-calculus [Correa_Bareinboim_2020] inspired IPW and G-computation estimators for clinical utility, in addition to more standard IPW and G-computation estimators, in this setting. After proving consistency of each estimator for the clinical utility, we compare the finite sample properties of the estimators via simulation. Finally, we construct double-robust estimators using the IPW and G-computation estimators, again investigating the finite sample properties via simulation.

Day: Wednesday, Board 19, Side B

Title: Development process of a directed acyclic graph (DAG) to investigate the influence of executive functioning on the maintenance of high impact chronic pain

Presenter: Annick De Paepe

Affiliation: Ghent University

Coauthors: Anna Gibby, Laura Carolina Oporto Lisboa, Matthew Nunes, Emma Fisher, Edmund Keogh, Christopher Eccleston & Geert Crombez

Abstract: In applied health research we are often interested in causal questions. Directed Acyclic Graphs (DAGs) have been developed as an intuitive tool to identify the sufficient adjustment set and provide a clear basis for constructive discussions among researchers. Unfortunately, the uptake of DAGs within applied health research is limited. Moreover, when DAGs are used, researchers fail to report how they constructed it. Here, we describe the process of developing a DAG for the influence of executive functioning on the maintenance of chronic high impact pain. The DAG was built based on domain knowledge (i.e. top down), which was obtained from the literature, researchers, and patients with chronic pain in four phases: (1) Brainstorming phase; (2) Refinement phase; (3) Exposition phase; (4) Reconciliation phase (Rodrigues et al., 2022). In the meeting of researchers, 5 steps were followed to construct the DAGs as outlined by a recent scoping review on guidelines for DAG development (Poppe et al., submitted): (1) Specify research question and define the independent and dependent variable; (2) Add common causes and arrange temporally; (3) Draw forward arrows; (4) Add nodes representing selection procedures; (5) Add nodes representing measurement bias. The developed DAG is a useful tool to guide data-analysis for the present and future studies. In a next step, data from the UK Biobank will be used to answer the research question.

Day: Thursday, Board 1, Side A

Title: Bayesian principal stratification for time-to-event endpoints: application to principal strata defined by the occurrence of antidrug antibodies

Presenter: Emma Torrini

Affiliation: Department of Statistics, Computer Science, Applications, University of Florence, Florence, Italy

Coauthors: Fabrizia Mealli, Christian Stock

Abstract: Principal stratification has been proposed as one approach to deal with intercurrent events in the ICH E9 (R1) addendum. However, so far, limited experience exists with principal stratification in the context of pharmaceutical clinical trials, especially concerning situations where interest is in a time-to-event endpoint.Our work is motivated by questions arising in the development of biological drugs in rare immunological diseases, where patients under the investigational treatment may have an immune response that leads to the development of antidrug antibodies (ADAs). If ADAs occur, they can have an impact on the efficacy of the drug. It is thus commonly an important secondary objective in phase II/III trials to explore the efficacy of the drug in patients who develop ADAs. Specifically, it is of interest to estimate the effect of the drug in the principal stratum of patients who would develop ADAs if given treatment.We investigate a basic Bayesian principal stratification approach for exponentially distributed time-to-event endpoints that applies to the described setting. It is based on a latent mixture likelihood and allows consideration of predictors of ADA development. We focus on the estimation of hazard ratios and restricted mean survival times using MCMC methods. Our simulation results show that the methodology can validly estimate the parameters of interest. A publicly available R package is presented that facilitates model fitting and simulation to determine operating characteristics in a given setting.Overall, this work lays theoretical and practical foundations for desirable extensions, including the use of more flexible time-to-event distributions.

Day: Thursday, Board 1, Side B

Title: Interference and interpretable parameters in competitive healthcare markets

Presenter: Aaron Sarvet

Affiliation: EPFL: Ecole Polytechnique Federale de Lausanne

Abstract: When data arise from a competitive healthcare marketplace, independent and identically-distributed (IID) data models are rarely justified. Nevertheless, the extant literature formulates treatment allocation using conventional formalisms in causal inference: IID data, individualized-dynamic treatment regimes, and constrained optimization. Alternatively,

we formulate questions of policy learning and evaluation for treatment allocation in such settings within an interference framework. Insodoing, we illustrate conditions under which existing procedures obtain nominal numerical properties and interpretations. Specifically, we locate the statistical parameter of the conventional approach as a large-population limiting case of a functional identifying a more appropriate causal estimand under an elaborated causal and statistical model. Thereby, we justify the use of well-studied statistical procedures and inherited asymptotic properties for a more realistic setting, and also clarify when the use of such procedures is inappropriate. As a motivating example, we study the effect of prompt intensive care unit admission on 7-day survival using data from cohort study of 13,011 patients in 48 UK National Health Service hospitals.

Day: Thursday, Board 2, Side A

Title: Towards better understanding of different ways to tackle immortal time bias

Presenter: Johan Steen

Affiliation: Ghent University

Abstract: Immortal time bias, a type of bias which arises from conditioning on the future, has been identified and documented since the early 1970s. Different analytical solutions (developed either outside or within a formal causal framework) generally try to avoid conditioning on the future by either considering alternative time scales (e.g. landmarking approaches or emulation of nested trials) or (implicitly) considering hypothetical scenarios where all patients initiate treatment at baseline or remain untreated (e.g. the extended Kaplan-Meier estimator). Consequently, these different approaches rely on different sets of underlying assumptions and produce numerical results that carry different interpretations. Awareness about the potential for immortal time bias has increased in the medical literature in the past decade(s), and different analytical solutions proposed in the statistical literature, are increasingly being adopted in practice. Unfortunately, blunders against immortal time still find their way into high-impact journals and there is a general lack of understanding of the different analytical solutions, their underlying assumptions and their interpretational implications. Moreover, certain ad-hoc approaches to tackle immortal time bias that are being advocated in the medical literature may even inadvertently introduce other types of bias (such as selection bias).I aim to elucidate some of these often overlooked subtleties by means of a series of simulation experiments and an empirical example using hospital data and a negative control exposure. Building on earlier work by others, I aim to shed light on the estimands that are (implicitly) targeted by different approaches and on their connection with observational target trial emulation.

Day: Thursday, Board 2, Side B

Title: Testing and estimation of treatment effects in data with spatio-temporal dependence

Presenter: Amit Sawant

Affiliation: EPFL, Switzerland

Abstract: Researchers are often interested in answering causal questions from observational data where i.i.d. assumptions fail. Studies of infectious diseases and social networks are canonical examples, but different violations of i.i.d. assumptions are pervasive in other applied sciences, such as biology, ecology and meteorology. These violations frequently co-occur with unmeasured confounding. Motivated by a study of vehicle traffic on local animal behaviour, we define assumptions that allow hypothesis testing and effect estimation in confounded spatio-temporal data. In particular, we suggest permutation tests for the sharp null hypothesis of no exposure effect, which are insensitive to either spatial or temporal violations of i.i.d. assumptions. This test also incorporates a difference-in-differences technique to handle unmeasured confounding. We further suggest estimators of the mean effect under additional structural assumptions. These methods are applied to longitudinal data of animal detections from motion-triggered camera traps in Banff National Park. While conventional methods fail in this example, we find a positive causal effect of reducing human activity on animal movement in Banff National Park.

Day: Thursday, Board 3, Side A

Title: Estimating the effect of a primary care access improvement programme on patient satisfaction: emulating a target trial using cluster-level data

Presenter: Yiwen Xu

Affiliation: London School of Hygiene & Tropical Medicine

Coauthors: Ruth Keogh; Geraldine Clarke; Karla Diaz-Ordaz; Jean Ledger; Minal Bakhai; Izzy Hatfield

Abstract: Healthcare policies are often introduced without randomised studies and their evaluation typically relies on observational data. We aim to use the target trial emulation (TTE) framework to estimate the effect of a primary care policy. While TTE has proven effective in evaluation studies focused on individual-level exposures, its application in cluster-level evaluation is relatively unexplored, and brings challenges such as staggered adoption and violations of the "no-interference" assumption.Our motivating example is an impact evaluation of the 2022 "Accelerate Access Improvement Programme (AAIP)" policy for general practices in England on patient satisfaction. We emulated a clustered randomised

trial to estimate the average treatment effects of AAIP, using practice-level data. To attenuate biases from model misspecification or regularisation in a high-dimensional setting, we explored collaborative targeted maximum likelihood estimation (CTMLE), in which variable selection for the treatment model is adaptive to the outcome. This was compared with some well-studied approaches, including outcome regression, inverse probability weighting estimators and TMLE.It was hypothesised that the effects of AAIP could be heterogeneous according to practice characteristics such as practice size, rate of workforce and location (urban/rural). To explore this, we implemented a data-driven approach using a causal forest, which accommodates non-linearities naturally and provides variable importance rankings for heterogeneity in a single output.We found no significant evidence that AAIP improved patient satisfaction. We also found no significant effect heterogeneity across all covariates. Our work provides a practical example of implementing the TTE framework and machine-learning-based causal inference methods for health policy evaluation.

Day: Thursday, Board 3, Side B

Title: Implications of the estimand framework for the imputation and analysis of quality of life in single-arm trials

Presenter: Doranne Thomassen

Affiliation: Leiden University Medical Center

Coauthors: Dries Reynders, Satrajit Roychoudhury, Cecilie Delphin Amdal, Jammbe Z. Musoro, Willi Sauerbrei, Els Goetghebeur, Saskia le Cessie; on behalf of SISAQOL-IMI Work Package 3

Abstract: Single-arm trials are gaining importance in the evaluation of oncology treatments. Results from such trials require careful interpretation, which benefits from structured causal thinking and a clearly defined estimand. In particular, this holds for repeatedly measured patient-reported outcomes such as quality of life. In our case study, we aimed to show the implications of the ICH E9 (R1) estimand framework for the imputation, analysis and interpretation of global quality of life in a single-arm trial setting. For the longitudinal global quality of life outcome in a single-arm cancer trial, we presented a range of possible estimands, each suitable for different clinical research aims. We focused on varying the choice of the variable of interest and strategies to deal with intercurrent events (death, treatment discontinuation and disease progression). Statistical methods were described for the estimation of each estimand, with attention to missing data methods, and the corresponding results on the trial data were shown. The results show that decisions made in the estimand framework are not trivial and often-used analysis methods for longitudinal data may not correspond to the intended estimand. The estimand framework provides a structure to match a research question with a clear target of estimation, supporting specific clinical decisions. Adherence to this framework

can help improve the quality of data collection, analysis and reporting of single-arm trials, impacting decision making in clinical practice.

Day: Thursday, Board 4, Side A

Title: Estimating Causal Effects on a Sample of Networked Population

Presenter: Bar Weinstein

Affiliation: Tel Aviv University

Coauthors: Daniel Nevo

Abstract: Estimating causal effects in the presence of interference, where the treatment of interest spreads through a network of units, is a nascent topic in causal inference. Existing studies often assess these effects on a sampled subset, assuming that the observed network accurately captures the interference structure. However, the observed network is typically obtained via network sampling design and may, thus, misrepresent the true interference structure because not all nodes and edges are fully observed.We address the challenge of estimating causal effects on a sample obtained through various network sampling designs. We first show that in observational studies it is a formidable task due to potential interference between recruited and non-recruited units. We then consider experiments in which treatment is randomized only for recruitedunits and show that the identification of effects requires additional assumptions on the network sampling design, exposure mapping, and network model.To address these issues, we propose a model-based Bayesian framework and an estimation procedure of causal effects that account for uncertainty arising from both network sampling and random error. The procedure is flexible and can accommodatevarious network sampling designs, as well as network and outcome models. A simulation study illustrates the estimation error resulting from neglecting network sampling and the benefit of explicitly accounting for it. We apply our proposed methods to an HIV-prevention trial (HPTN 037) that employed an egocentric network sampling design for unit recruitment.

Day: Thursday, Board 4, Side B

Title: A causal inference approach to estimating under-treatment in elderly lung cancer patients in population-based observational cancer registry data

Presenter: Finian Bannon

Affiliation: Queen's University Belfast

Coauthors: Abdul Qadr Akinoso-Imran, Frank Kee, Gerry Hanna, Niall McGonigle, Colin Fox, Anna Gavin

Abstract: Age-related under-treatment can occur in the absence of adequate assessment when clinical decision-making relies on cancer patient age rather than on clinical covariates that affect excess cancer mortality rates such as disease stage, frailty, and comorbidities. The study provides a definition of undertreatment, its statistical identification using a Directed Acyclic Graph, and a g-computation method to estimate it. Undertreatment can be defined as the proportion of the net survival deficit, between younger and older lung cancer patients, that is mediated through older patients' lower treatment rates, when compared to the younger, within subgroups defined by clinical covariates. In a Directed Acyclic Graph, this definition identifies with one component of the Natural Indirect Effect (NIE) from age (exposure) to treatment (mediator) to net survival (outcome). The other component of the NIE, the pathway from age to clinical covariate (intermediate confounder) to treatment to net survival, contributes, along with the Natural Direct Effect, to the 'acceptable' proportion of net survival deficit that is not attributed to under-treatment. To estimate under-treatment, g computation is adopted to 1) model causal relationships flexibly, 2) accommodate effect modification of age on treatment or outcome by clinical covariate, 3) incorporate imputation of missing clinical data 'accommodating the substantive models', 4) handle intermediate confounders, and 5) estimate standard errors using bootstrap methods. The estimation of undertreatment is applied to a population-based cancer registry dataset of 4,232 lung cancer patients diagnosed in Northern Ireland between 2012-2015 who potentially received either surgery, radiotherapy, or chemotherapy.

Day: Thursday, Board 5, Side A

Title: Data-adaptive inference for causal parameters in right-censored competing risks data using the state learner

Presenter: Anders Munch

Affiliation: Section of Biostatistics, University of Copenhagen

Coauthors: Thomas Gerds

Abstract: The framework of targeted machine learning provides a general methodology for obtaining valid statistical inference for causal parameters when data-adaptive methods are used. In particular, a super learner can be used to perform model selection, providing a general method for obtaining valid statistical inference without relying on a single pre-specified model. Super learning assesses model performance using cross-validation. Cross-validation based on right-censored data typically relies on a pre-specified model for the censoring distribution, which can be difficult to provide, especially for observational data. To alleviate this, we propose a new super learner, the state learner, which jointly assesses the performance of models for both the outcome and the censoring distributions. The state learner uses the data to select a pair of models that are optimal for predicting the state-occupation probabilities

that characterize the observed data distribution. The state learner readily extends to settings with competing risks and is particularly well suited to be used in combination with targeted learning. We demonstrate how the state learner can be used to obtain estimates of various low-dimensional target parameters defined in a competing risks model. We apply our method to analyze the causal effect of bystander interventions on out-of-hospital cardiac arrest.

Day: Thursday, Board 5, Side B

Title: Robust Development of Individual Treatment Rules from Observational Data using Causal Bounds

Presenter: Gustav Jonzon

Affiliation: Department of Medical Epidemiology and Biostatistics, Karolinska Institutet

Coauthors: Michael C Sachs, Erin E Gabriel

Abstract: Complete Blood Counts (CBC) are often measured routinely in primary care. Some CBC signatures have shown strong correlation with development of hematological malignancy. The use of such signatures for early detection and intervention may benefit near-term survival. We have observational data on CBC-measurements in primary care and aim to develop an individual treatment rule (ITR) for optimal referral to a hematological specialist for further diagnostic investigation given their CBC values. We aspire to assign the referral decision to an individual given their set of CBC values that optimizes the expected conditional average treatment effect on 5-year survival. Doing so with observational data is challenging because unmeasured confounding makes average treatment effects nonidentifiable. We assume access to an instrumental variable, which in our motivating example is the historical referral rate by each general practitioner. This does not solve the nonidentifiability problem but does allow us to derive informative bounds. We propose to use nonparametric bounds on the conditional average treatment effects as the basis for optimization of our ITR. We extend the framework of Pu and Zhang(1) by incorporating additional covariates beyond the few expected to be available for decision-making and by moving beyond support vector machines for the optimization. We compare the performance of our ITR to one previously developed based on a (non-causal) prognostic prediction model. 1: "Estimating Optimal Treatment Rules withan Instrumental Variable: A Partial Identification Learning Approach, Journal of the Royal Statistical Society Series B: Statistical Methodology, 83.2 (Mar. 2021)

Day: Thursday, Board 6, Side A

Title: Using Prognostic Propensity Scores in Causal Inference with Observational Data

Presenter: Pablo Geraldo

Affiliation: Nuffield College, University of Oxford

Coauthors: Chad Hazlett (UCLA), Leonard Wainstein (Reed College)

Abstract: Since the seminal work of Rosenbaum and Rubin (1983), the propensity score has played a major role in improving causal effect estimation with observational data. Propensity scores have been used for stratification, matching, and weighting, to improve expected balance in the distribution of covariates across groups. More recently, balance estimators that directly target balance through calibration or optimization have gained acceptance due to their superior in-sample performance.While one of the primary strengths of these balancing methods lies in reducing the reliance on a correctly specified outcome model, one of their drawbacks is their relative inefficiency resulting from indiscriminately balancing across covariates of dissimilar importance. An advisable alternative is to utilize prognostic scores (predicted untreated potential outcomes given covariates) to augment the weighting estimator, thereby recovering some lost efficiency without purely depending on an outcome model. Others have argued for two-step estimators that, first, either select a subset of covariates to balance or assign different importance to different covariates, and then use this information to implement a restricted balancing step.In this paper, we demonstrate the use of a prognostic propensity score (PPS) as a conceptually simple yet effective alternative to traditional propensity score-based methods. Instead of predicting the treatment status given covariates, the PPS does so based on estimates of the control potential outcome, addressing only the portion of imbalance relevant to de-biasing the treatment effect of interest. We compare the performance of PPS-based regression, matching, and weighting analyses with other causal effect estimators through simulations and an empirical application, illustrating that the method can offer a practical alternative for researchers dealing with hard-to-balance and distracting covariates.

Day: Thursday, Board 6, Side B

Title: Causal-DRF: Conditional Kernel Treatment Effect using Distributional Random Forest

Presenter: Jeffrey Näf

Affiliation: Inria

Abstract: A frequent measure to assess the effectiveness of a treatment given some covariates is the conditional average treatment effect (CATE), the difference in conditional expectation of the counterfactuals. However, the effects of a treatment might extend beyond the conditional expectation. Inspired by causal forests for CATE estimation, we develop a forest-based method to estimate the conditional kernel treatment effect (CKTE), based on the recently introduced Distributional Random Forest (DRF) algorithm. Adapting the splitting criterion of DRF, we show how one forest fit can be used to obtain a consistent estimator, as well as an approximation of its sampling distribution. This allows, in particular, to construct a conditional kernel-based test for distributional effects with provably valid type-I error. Finally, we introduce a

theoretically motivated variable importance measure for this new Causal-DRF. We illustrate the effectiveness of the new approach on several simulated and real data examples.

Day: Thursday, Board 7, Side A

Title: On the possibility of doubly robust root-n inference

Presenter: Matteo Bonvini

Affiliation: Rutgers, The State University of New Jersey

Coauthors: Edward H. Kennedy, Oliver Dukes, and Sivaraman Balakrishnan

Abstract: We study the problem of constructing an estimator of the average treatment effect (ATE) that exhibits doubly-robust asymptotic linearity (DR-AL). This is a stronger requirement than doubly-robust consistency. In fact, a DR-AL estimator can yield asymptotically valid Wald-type confidence intervals even in the case when the propensity score or the outcome model is inconsistently estimated. On the contrary, the celebrated doubly-robust, augmented-IPW estimator requires consistent estimation of both nuisance functions for root-n inference. Previous authors have considered this problem (van der Laan, 2014, Benkeser et al, 2017, Dukes et al 2021) and provided sufficient conditions under which the proposed estimators are DR-AL. Such conditions are typically stated in terms of "high-level nuisance error rates" needed for root-n inference. In this paper, we build upon their work and establish sufficient and more explicit smoothness conditions under which a DR-AL estimator can be constructed. We also consider the case of slower-than-root-n convergence rates and study minimax optimality within the structure-agnostic framework proposed by Balakrishnan et al (2023). Finally, we clarify the connection between DR-AL estimators and those based on higher-order influence functions (Robins et al, 2017) and complement our theoretical findings with simulations.

Day: Thursday, Board 7, Side B

Title: Sensitivity analysis with multiple treatments and multiple outcomes with applications to air pollution mixtures

Presenter: Joseph Antonelli

Affiliation: University of Florida

Coauthors: Suyeon Kang, Alexander Franks

Abstract: Understanding the health impacts of air pollution is vital in public health research. Numerous studies have estimated negative health effects of a variety of pollutants, but accurately gauging these impacts remains challenging due to the potential for unmeasured confounding bias that is ubiquitous in observational studies. In this study, we develop a

framework for sensitivity analysis in settings with both multiple treatments and multiple outcomes simultaneously. This setting is of particular interest because one can identify the strength of association between the unmeasured confounders and both the treatment and outcome, under a factor confounding assumption. This provides informative bounds on the causal effect leading to partial identification regions for the effects of multivariate treatments that account for the maximum possible bias from unmeasured confounding. We also show that when negative controls are available, we are able to refine the partial identification regions substantially, and in certain cases, even identify the causal effect in the presence of unmeasured confounding. We derive partial identification regions for general estimands in this setting, and develop a novel computational approach to finding these regions.

Day: Thursday, Board 8, Side A

Title: Causal discovery for nonlinear mixed-scale data

Presenter: Luca Bergen

Affiliation: Leibniz Institute for Prevention Research and Epidemiology – BIPS

Coauthors: Vanessa Didelez, Marvin N. Wright

Abstract: Causal discovery is used in the life sciences to obtain insights into the causal structure among a set of random variables. However, the data – as collected in cohort studies, for example – can pose considerable challenges for causal discovery methods as they often consist of mixed-scale variables with nonlinear dependencies. In recent years, several methods have been proposed to deal with these challenges. They comprise both score-based methods (e.g. MVP, Andrews et al. 2018) and nonparametric conditional independence tests for use in constraint-based causal discovery algorithms (e.g. GCM, Shah & Peters 2020 or RCIT, Strobl et al. 2019). Due to a lack of general theoretical results and the diversity of possible nonlinear data-generating processes, there is no optimal method which can be recommended in general. Therefore, users typically have limited information about which methods to choose.Our contribution is twofold. We conduct a detailed comparison of the method's theoretical properties, where known, and empirical finite sample behavior in a simulation study. By assessing different data-generating processes and varying levels of nonlinearity, our study aims to inform applied researchers regarding the level of errors these methods can incur and serves as a guide for deciding which methods to apply. Furthermore, we propose CPI (Watson & Wright 2021) for causal discovery, a conditional independence test based on supervised learning, by augmenting it for marginal testing. CPI employs flexible machine learning models for all variable types, providing a suitable method for use on nonlinear mixed-scale data.

Day: Thursday, Board 8, Side B

Title: Sensitivity of modified treatment policy estimates to positivity violations and sparsity issues in continuous treatments: introducing a diagnostic tool

Presenter: Katharina Ring

Affiliation: Ludwig-Maximilians-Universität München

Coauthors: Michael Schomaker

Abstract: The positivity assumption requires that all treatment levels of interest can potentially be observed for every individual and is typically necessary to ensure the identifiability of causal effects. We examine positivity definitions, violations, and implications for estimands in the context of continuous interventions, for which this assumption is less often discussed. Our focus lies on modified treatment policies (MTPs), which have been proposed as a possible solution when dealing with positivity issues.We conducted simulation studies comparing the bias of MTPs and static intervention schemes for varying degrees of positivity violations. Our results show that MTPs, depending on the specific estimands defined, can encounter equal or even heightened positivity-related challenges during estimation. This can often be attributed to the fact that, irrespective of the type of intervention scheme, a new assigned treatment can lack data support given an observation's covariates. To address this issue, we present a diagnostic tool to help detect positivity issues, which is not limited to MTP estimands. This tool assesses, for each observation, the quantity of similar observations that received a comparable treatment, thereby gauging data support for estimating the outcome. Therefore, it provides a local evaluation tailored to a specific estimand. The diagnostic serves three purposes: firstly, quantifying the extent to which data sparsity compromises estimation; secondly, aiding decisions on restricting the sample to adequately supported observations; and thirdly, guiding the formulation of a better estimable intervention scheme, for instance by defining a data-adaptive MTP using the diagnostic, ensuring the desired data sparsity requirements.

Day: Thursday, Board 9, Side A

Title: Instrumental Variable Estimation of Distributional Causal Effects

Presenter: Lucas Kook

Affiliation: University of Copenhagen

Coauthors: Niklas Pfister

Abstract: Distributional causal effects extend the more established average causal effect by describing how the entire distribution of a response changes under interventions. In survival analysis, for instance, the distributional causal effect describes differences in t-year survival

probabilities instead of the less informative difference in conditional mean survival times (the latter may not even be well-defined in the presence of censoring). While distributional causal effects are readily estimated with conventional statistical techniques in data from randomized controlled trials, estimating them in settings with with non-compliance or in the presence of unmeasured confounding is considerably more challenging. A promising approach is to adapt instrumental variable (IV) estimation, which is well-established for estimating average causal effects in the presence of unobserved confounding, to estimating distributional causal effects. Starting from a nonparametric IV model, we show that the interventional cumulative distribution function (which characterizes the distributional causal effect) is the only function that, when evaluated at the observed response and treatment, yields a random variable which is simultaneously uniformly distributed and independent of the instrument. Based on this identification approach we propose a nonparametric estimator for the distributional causal effect. We compare our proposed estimator with related IV-based procedures and illustrate the proposed estimator in simulations and a real-data application.

Day: Thursday, Board 9, Side B

Title: The relevance of causal thinking for experience sampling methods study design

Presenter: Louise Poppe

Affiliation: Department of Public Health and Primary Care (Ghent University)

Coauthors: De Paepe Annick, Van Cauwenberg Jelle, Deforche Benedicte, Van Dyck Delfien, & Crombez Geert

Abstract: IntroductionWithin applied health research, studies using intensive longitudinal methods, also termed diary or experience sampling methods (ESM) studies, are highly popular to examine within-person associations. Typically these studies focus on potential targets for interventions and their outcomes (e.g., physical activity (PA) and cognitive performance), but do not account for within-subject sources of confounding. The aim of this study was to gain insight in the potential confounding pathways between PA and cognitive functioning at the within-subject level among older adults by developing a directed acyclic graph (DAG) based on literature and expert consultation.MethodsThe evidence synthesis method proposed by Ferguson et al. (2020) was used to derive relevant information from available empirical studies. None of the identified ESM studies examining the effect of PA on cognitive functioning at the within-person level took into account within-subject variables. Hence, six experts in the domain of PA and/or cognitive functioning among older adults were individually interviewed to identify within-subject sources of confounding. Experts unfamiliar with DAGs first received a short introduction to the general concepts of causal inference and the role of DAGs herein.ResultsA large number of within-subject sources of confounding was identified by the experts. Often mentioned confounders were fatigue, stress and pain. Based on the obtained information the final DAG was created.ConclusionsThe developed DAG is a useful tool to discuss sources of

confounding in ESM studies and to visualize the benefits of using experimental methods (e.g., within-participant encouragement design) to eliminate this confounding bias.

Day: Thursday, Board 10, Side B

Title: Approximate Balancing Weights for Clustered Observational Study Designs

Presenter: Luke Keele

Affiliation: UPenn

Coauthors: Eli Ben-Michael

Abstract: In a clustered observational study, a treatment is assigned to groups and all units within the group are exposed to the treatment. We develop a new method for statistical adjustment in clustered observational studies using approximate balancing weights, a generalization of inverse propensity score weights that solve a convex optimization problem to find a set of weights that directly minimize a measure of covariate imbalance, subject to an additional penalty on the variance of the weights. We tailor the approximate balancing weights optimization problem to the clustered observational study setting by deriving an upper bound on the mean square error and finding weights that minimize this upper bound, linking the level of covariate balance to a bound on the bias. We implement the procedure by specializing the bound to a random cluster-level effects model, leading to a variance penalty that incorporates the signal-to-noise ratio and penalizes the weight on individuals and the total weight on groups differently according to the the intra-class correlation.

Day: Thursday, Board 11, Side A

Title: Applying difference-in-differences to stepped wedge designs with varying intervention intensity: peer support and Hepatitis C elimination.

Presenter: Constantin Schmidt

Affiliation: University of Cambridge

Coauthors: Pantelis Samartsidis (University of Cambridge); Shaun Seaman (University of Cambridge); Beatrice Emmanouil (NHS England); Leila Reid (Hepatitis C Trust); and Daniela De Angelis (University of Cambridge)

Abstract: We consider the estimation of intervention effects in stepped wedge designs with non-random assignment into an intervention with multiple levels of intervention intensity. As our motivating example, we investigate the effect of peer support on the number of people successfully treated for Hepatitis C Virus (HCV) infection in England. Anti-HCV treatment can clear the virus and reduce transmission. People who inject drugs (PWID) are at high

risk of HCV infection through needle sharing. However, PWID are difficult to engage. Thus, since 2018, Operational Delivery Networks (ODNs) administering anti-HCV therapy have progressively adopted peer support. Peers are community-based individuals with lived experience of HCV who can encourage participation in and adherence to treatment. Our data consists of monthly observations on all 22 English ODNs between June 2016 and August 2022.Since intervention assignment was non-random and intervention effects might be heterogeneous, the standard model for randomised stepped wedge designs, a linear mixed effects model, would be likely to yield biased intervention effect estimates. So instead, we apply linear imputation difference-in-differences (DiD) which allows selection into intervention to depend on unobserved, time constant factors and for intervention effects to be heterogeneous across units and time. Peer support was associated with an increase of 4.20 individuals successfully completing treatment per ODN per month (95%-CI: 1.61–8.33; p=0.003) compared to no peer support. The effect of peer support increased with time in intervention. In ongoing work, we expand staggered adoption DiD methods by investigating how the intervention effect varies with number of peers employed.

Day: Thursday, Board 11, Side B

Title: Causal uplift modelling of hemodynamic treatment and acute kidney injury in Anaesthesiology

Presenter: Markus Huber

Affiliation: Department of Anaesthesiology and Pain Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

Coauthors: Patrick Y. Wuethrich

Abstract: In clinical medicine, postoperative acute kidney injury (AKI) remains a common major adverse event after surgery. However, causal analyses of the underlying cause-effect relationships are missing. We thus aim to investigate the potential of uplift modelling–a framework combining causal inference and machine learning–in identifying patients for which certain hemodynamic treatment regimes result in an AKI-free postoperative period. We use data from a cystectomy database at our tertiary hospital. The primary outcome was no AKI postoperatively and treatment refers to a dichotomized total intraoperative fluid balance (TIFB) and norepinephrine (NE) regime. Based on a clinically motivated causal graph, the average treatment effect (ATE) was calculated with an IPTW pseudo-population. Uplift was computed with a two-model approach using random forests.The ATE was 8.6% in favour of a high TIFB/low NE treatment. The uplift decile chart shows that the uplift model was able to select subgroups of patients who benefited from a high TIFB/low NE treatment. The uplift model features an Area Under the Qini Curve (AUQC) of 26.9, highlighting the model's ability to rank patients according to their expected treatment benefits.In this work of progress, we conclude that uplift modelling has the potential to select subgroups of patients for which

a given fluid-NE regime results in an AKI-free recovery, thus allows moving towards a more personalized care delivery in Anaesthesiology.Given the challenging perioperative setting with time-dependent confounding and treatment at irregular intervals, we would look forward to discussing causal inference methods in Anaesthesiology with the EUROCIM participants.

Day: Thursday, Board 12, Side A

Title: An Efficient Estimator for Multistate Event History Data

Presenter: Gergely Dániel Lukáts

Affiliation: University of Oslo

Coauthors: Kjetil Røysland, Pål Christie Ryalen, Niklas Nyboe Maltzahn

Abstract: We know the Aalen-Johansen estimator as a standard estimator for causal inference on multistate models based on event history data. This estimator is root-n consistent under the assumption of independent censoring. However, it is not necessarily efficient! Our research focuses on developing a modified, efficient estimator.If we assume that the system is causal with respect to an intervention that would prevent censoring, we can calculate efficient influence functions where the intensity for censoring is a nuisance parameter.By treating the influence functions as estimating equations (for example) we can derive a new estimator. We will discuss efficiency, robustness and Neyman orthogonality of the Aalen-Johansen estimator and the new estimator under the given censoring scheme, as well as simulation examples.

Day: Thursday, Board 12, Side B

Title: Implied Weights of Estimators for (Conditional) (Local) Average Treatment Effects

Presenter: Michael Knaus

Affiliation: University of Tuebingen

Abstract: Estimators that can be represented as weighted observed outcomes are very useful in practice. Their (implied) weights allow, e.g. to check covariate balancing, detect extreme weights, or to characterize target populations like the compliers in instrumental variables settings. This paper provides a unified framework for a range of common estimators and shows under which conditions their implied weights are defined. The framework recovers results from the literature as special cases and allows to establish several new results. In particular the paper spans parametric estimators like OLS and TSLS, semi-parametric estimators like (augmented) inverse probability weighting (IPW) and partially linear regression for (local) average treatment effects, as well as causal machine learners like causal forest and DR-learner for conditional (local) average treatment effects. We analyze basic properties of the weights in

the binary treatment case and find, e.g. that weights of augmented IPW sum up to one for the treatment and control groups even without normalized IPW weights, while they do not sum up to one for partially linear regressions. The latter explains the puzzle that estimators building on partially linear regressions like causal forest are sensitive to scaling of the outcome and fail to recover the correct effects even in very simple data generating processes where every unit has the same deterministic potential outcomes. The closed form representation of the implied weights highlights the mechanisms behind this behavior and hints at potential fixes beyond a brute force weights normalization following Hajek (1971).

Day: Thursday, Board 13, Side A

Title: Bayesian Multivariate Synthetic control for correlated outcomes

Presenter: Giulio Grossi

Affiliation: University of Florence

Abstract: The Synthetic Control Method (SCM) is a widely recognized tool in causal inference for estimating effects in panel data settings. An underdeveloped aspect is the use of SCM in settings where multiple outcomes are simultaneously exposed to the active treatment. This setting can be common in applied fields, such as economics, policy evaluation, epidemiology, or clinical studies. Traditionally, SCM estimates are calculated separately for each outcome. In this work, we propose an expansion of the current methods to deal with correlated outcomes: we estimate the outcomes weights at the same time, leveraging the correlation structure across the multiple outcomes.Our focus is on scenarios where a specific treatment impacts several interconnected outcomes. We posit that synthetic control weights for two outcomes should correlate more as their pre-treatment relationship strengthens. We employ a Bayesian Multivariate model to achieve this, utilizing Gaussian process priors for a flexible, semiparametric estimation of outcomes weights.We discuss the theoretical properties of the estimator, and validate this methodology through several simulation scenarios, providing a broad application framework.Our motivating application is the so-called Iberian Exception, the mechanism implemented by Spain in 2022 to set a cap for natural gas prices exploited in energy production. These interventions, starting with energy prices, have multiple impacts on other macroeconomic measures, such as GDP and unemployment. Here we evaluate the overall assessment of the policy on multiple outcomes.

Day: Thursday, Board 13, Side B

Title: Simulations to improve the rigor & reproducibility of real-data applications

Presenter: Nerissa Nance

Affiliation: UC Berkeley

Coauthors: Maya Petersen, Mark van der Laan, Laura Balzer

Abstract: The Roadmap for Causal Inference outlines a systematic approach to our research endeavors: define the effect of interest, evaluate needed assumptions, conduct statistical estimation, and carefully interpret results. At the estimation step, it is essential that the estimation algorithm be carefully pre-specified to optimize its expected performance for the specific real-data application. Simulations that realistically reflect the application, including key characteristics such as strong confounding and rare or missing outcomes, can help us gain a better understanding of an estimator's performance and achieve this goal. We illustrate this with two examples, using the Causal Roadmap and realistic simulations to inform estimation selection and full specification of the Statistical Analysis Plan. First, in an observational longitudinal study, outcome-blind simulations are used to inform nuisance parameter estimation and variance estimation for longitudinal targeted maximum likelihood estimation (TMLE). Second, in a cluster-randomized control trial with missing outcomes, exposure-blind simulations are used to ensure control for type-I error in Two-Stage TMLE. In both examples, realistic simulations empower us to pre-specify an estimator that is expected to have strong finite sample performance and also yield quality-controlled computing code for the actual analysis. Together, this process helps to improve the rigor and reproducibility of our research.

Day: Thursday, Board 14, Side A

Title: Optimized Weighting in Tree-based Methods

Presenter: Karolina Gliszczynska

Affiliation: University Duisburg-Essen

Abstract: To obtain an unbiased estimator of a causal effect in the absence of randomized controlled and natural experiments, it is essential to balance the distributions of observable covariates between the treated and control groups. Various methods exist to achieve this balance, including optimization-based approaches recently proposed in the causal inference literature. Although optimization-based methods have demonstrated an improved ability to balance covariate distributions and estimate causal effects, there needs to be more awareness of integrating these two fields. The conventional approach typically involves a weighted sample difference, with limited regard for integrating these weights into more sophisticated modeling frameworks. We present a perspective by integrating optimization-based weighting methods with established machine learning methods, leveraging the optimized weights as supplemental features within tree-based algorithms. Specifically, we introduce two strategies for that. In the first approach, we use the optimized weights as simple sample weights in the causal forest algorithm. In the second approach, we use these weights to replace the propensity score within the X-Metalearner algorithm. We show that both approaches perform well in low and high-dimensional settings and are particularly interesting in scenarios where the classical propensity score is close to 0 and 1, potentially leading to extreme inverse

probability weights. A suitable application herein lies in natural experiments within health and social sciences, where, due to ethical reasons, the control or the treated group is much larger than the other group.

Day: Thursday, Board 14, Side B

Title: Bounds for selection bias using outcome probabilities

Presenter: Stina Zetterstrom

Affiliation: Department of Statistics, Uppsala University

Abstract: The selection of subjects into the study population, either voluntary or involuntary, may result in selection bias in the estimates. To assess the robustness of the estimates and the magnitude of the bias, bounds for the bias can be calculated. Previously reported bounds for selection bias, for instance, the bounds by Smith and VanderWeele (SV) presented in 2019, often require the specification of unknown relative risks that can be difficult to provide. Alternatively, assumption-free (AF) bounds for the selection bias were recently proposed by Zetterstrom and Waernbaum, but they can be non-informative in some cases. Here, I derive new bounds that are expressed using observed data and unobserved outcome probabilities, which may be easier to specify than unknown relative risks. The previously reported AF bounds are special cases of the new bounds when the sensitivity parameters are set to their most conservative values. The previously reported and new bounds are compared in a simulation study. Depending on the data generating process and causal estimand, the proposed bounds can be tighter or wider than the reference SV and AF bounds. Importantly, in cases with sufficiently common outcome and exposure, the proposed bounds are often informative, especially for the risk difference in the total population. It is worth stressing that, even in cases where the new bounds are wider than the reference bounds, the proposed bounds based on unobserved probabilities may be easier to specify than the reference bounds based on unknown relative risks.

Day: Thursday, Board 15, Side A

Title: PerturbSCM: Benchmarking Causal Structure Learning for Gene Perturbation Screens

Presenter: Luka Kovačević

Affiliation: MRC Biostatistics Unit, University of Cambridge

Coauthors: Sach Mukherjee, John Whittaker

Abstract: Technological advancements now allow large-scale interventional experiments to be carried out at the single-cell level. Of key interest is the gene regulatory network that governs relationships between measurements of gene expression. Despite ongoing theoretical and methodological advances in causal structure learning (CSL), performance of CSL methods under real world conditions and limitations remains incompletely understood and there is currently no clear consensus on performance in the context of large-scale perturbation studies in biology. To address this, we propose PerturbSCM, a framework for simulating observational and interventional data from single-cell RNA sequencing (scRNA-seq) experiments given a causal graph structure. Our approach (i) adheres to established domain knowledge regarding the distributions generated by scRNA-seq experiments, (ii) generates non-varsortable data, and (iii) enables statistical matching of the simulated distributions to real-world data. PerturbSCM relies on a zero-inflated Negative Binomial model for each node and a sigmoid function that represents the multiplicative regulatory effect of parents. Further, this structure ensures that regulatory effect and mean expression are independent and reduces the varsortability of simulated data. We show that PerturbSCM better reflects domain knowledge regarding effect propagation through a causal graph and how causal parents interact under intervention. We provide a Python implementation of PerturbSCM that allows for simulation with off-target effects, failed interventions and technical variation reflecting real-world data. PerturbSCM provides a framework for determining how well CSL algorithms work in specific settings, which is essential to applying CSL in the real-world. We present initial results on the performance of commonly used structure learners.

Day: Thursday, Board 15, Side B

Title: Accounting for confounders in longitudinal clinical trial data with pharmacometrics modeling, using latent conditional exchangeability

Presenter: Thomas Dumortier

Affiliation: Novartis Pharma AG, Basel, Switzerland

Coauthors: Oliver Baerenbold, and Christian Bartels

Abstract: We look at the problem of estimating the causal dose response relationship from data of a clinical trial where treatment dose can be changed over time. These trials may be affected by treatment confounder feedback. Standardization using sequential conditional exchangeability can in some situations be used to correct for the confounding, i.e., by conditioning on earlier responses. But there are situations where sequential conditional exchangeability does not hold or the high dimensionality of the conditioning set is challenging. Pharmacometrics models may provide a solution in the latter situations. Those are semi-mechanistic models, based on pharmacological principles thus particularly adapted to dose-response analyses. They combine population and individual (i.e., random) response parameters with a residual error model. The individual response parameters describe the

individual patient response and thus can be used to predict potential outcomes under different hypothetical treatment regimens. If the residual errors can be assumed uncorrelated or dose adaptations do not depend on the residual error, the individual parameters are blocking the confounding pathways ensuring latent conditional exchangeability.However, for pharmacometrics models, it has not been established how much data must be available to estimate the causal dose-response effect (practical identifiability) and which estimation methods are adequate (e.g., EBEs, SAEM, Bayes, …). While the principle of using pharmacometrics models as a solution to tackle causal problems has been discussed in seminal papers 30 years ago, their practical identifiability in presence of confounding has not been subject to academic research. Our intention is to revive those discussions.

Day: Thursday, Board 16, Side A

Title: Formalization of the causal interpretation of accelerated failure time models in the presence of unmeasured heterogeneity

Presenter: Mari Brathovde

Affiliation: Oslo University Hospital

Coauthors: Hein Putter, Morten Valberg, Richard Post

Abstract: In the presence of unmeasured heterogeneity, the hazard ratio for exposure is known to have a complicated causal interpretation. It is often suggested that this problem can be overcome by comparing the survival curves or by modeling the treatment's effect on the survival time ratio scale, specifically by employing accelerated failure time (AFT) models. Using an AFT model has the advantage of allowing straightforward incorporation of confounder adjustment into the model. In this work, we formalize the causal interpretation of the acceleration factor estimand in AFT models. To do so, we study systems describing the causal effect of a binary exposure parameterized using structural causal models, and data observed under independent censoring. We prove that the acceleration factor yields an appropriate causal effect measure in the presence of frailty and treatment effect heterogeneity. For illustration, we simulate a system where both AFT and proportional hazard models apply and demonstrate how the acceleration factor better reflects the causal effect than the hazard ratio. Moreover, we extend the formalization of the causal interpretation for causal systems with time-dependent acceleration factors. For this scenario, we highlight an important finding: the inability to differentiate between a time-varying but homogeneous effect and the existence of unmeasured effect heterogeneity. Despite the positive findings on the causal interpretation of acceleration factors, we reveal challenges that may arise when solving the estimating equations in the presence of effect heterogeneity. Thus, practitioners should exercise caution when employing parametric estimators of the AFT estimands.?

Day: Thursday, Board 16, Side B

Title: Selective Randomization Inference for Adaptive Studies

Presenter: Tobias Freidling

Affiliation: University of Cambridge

Coauthors: Zijun Gao, Qingyuan Zhao

Abstract: Many clinical trials follow a design with multiple stages: After each stage, the data is provisionally analysed and – based on these results – the recruitment of participants for the next stage as well as the administered treatment is chosen adaptively. For instance, we may want to exclude poorly performing drugs early (multi-arm multi-stage trials) or gather more samples from a certain subpopulation that shows a potentially beneficial response (enrichment trials).Analysing such adaptive studies is challenging as the data is used twice: (1) for selection of the design of later stages and the null hypothesis, (2) for testing the null hypothesis with the data generated under the chosen design. Since the data generating mechanism and null hypothesis are not pre-specified, classical statistical methods do not provide valid inference. The literature on adaptive studies is aware of this issue; however, suggested solutions are often limited in scope and usually specific to a certain design. In this work, we propose a general framework for analysing adaptive studies that can handle all kinds of designs and adaptive choices. Our approach uses concepts from the post-selection inference literature to develop a selective randomization p-value. Noteably, we do not require any assumptions on the law of the outcomes and covariates or on the dependence structure between different participants. We show that our method improves power compared to other valid randomization tests while still controlling the selective type-I error. Moreover, we construct selective confidence intervals and discuss different algorithms to compute the selective randomization p-value.

Day: Thursday, Board 17, Side A

Title: Accounting for clustering and baseline covariates in randomized trials

Presenter: Muluneh Alene Addis

Affiliation: Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium

Coauthors: Kelly Van Lancker, Stijn Vansteelandt

Abstract: In response to recent guidance from the U.S. Food and Drug Administration, there has been a heightenedinterest in covariate adjustment within the analysis of randomized controlled trials for drugs and biologics,driven by the prospect of increased efficiency. This surge in interest is notably influenced by advancements in the causal inference literature, suggesting

that treatment effect estimators, relying on standardization or g-computation, exhibit robustness to model misspecification when applied to data from randomized experiments. However, the practical implementation of these strategies often overlooks the fact that such experiments are typically conducted across multiple patient centers. The resulting clustering introduces concerns regarding the validity of confidence intervals for the treatment effect or counterfactual means, as well as the efficiency of resulting estimators and the interpretation of the estimands targeted by such methods. In this presentation, we delve into these concerns, offering valuable insights and proposing strategies for robustand efficient covariate adjustment in multicenter randomized experiments.

Day: Thursday, Board 17, Side B

Title: Design-aware imputation of missing data: A target trial emulation for the effect of ADHD pharmacological treatment on academic achievement

Presenter: Tomás Varnet Pérez

Affiliation: Norwegian Institute of Public Health

Coauthors: Kristin Romvig Øvergaard, Arnoldo Frigessi & Guido Biele

Abstract: The target trial emulation framework aims to avoid common pitfalls in the analysis of observational data by designing its analysis as though it were a pragmatic randomized clinical trial. A key element of this design is establishing "time-zero", the time when eligibility criteria and assignment takes place. Disregarding time-zero during analysis can introduce bias into our estimates via assignment to treatment group based on future information or by conditioning on post-treatment variables. At the same time, a common issue in observational data is missing data, which is usually addressed via multiple imputation. Often, the imputation process is seen as a purely predictive task. However, ignoring the causal structure of the data could result in the imputed values introducing additional bias. Our study leverages national registry data to emulate a pretest-posttest control group design and estimate the intention-to-treat effect of ADHD medication on national test scores in children diagnosed with ADHD born between 2000 and 2007 in Norway. We implement a Bayesian joint multivariate model that includes both an outcome model and different imputation models for each imputed variable that takes into account the temporality fixed by the target trial protocol. Sensitivity analyses with use of negative control exposures, different eligibility criteria and different identifying strategies are also considered. We conclude that ADHD medication initiation shows no clinically relevant long-term effect on average on learning as measured by Norwegian national tests.

Day: Thursday, Board 18, Side A

Title: A Comparison of Causal Forests and the DR-Learner for Estimating Conditional Average Treatment Effects

Presenter: Qi Zhang

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Coauthors: Ya-Hui Yu, Ashley Naimi

Abstract: Conditional average treatment effects (CATEs) hold great promise for precision medicine, particularly in settings where effect modification is likely. Theoretical work has developed methods to estimate CATEs, including the double-robust (DR) learner and the causal forest algorithm. Here, we conduct a simulation study comparing the finite sample properties of the DR learner and the causal forest algorithm. We explore performance in a range of scenarios with a binary effect modifier and when a set of conditioning variables are included with varying degrees of effect modifiers present. Scenarios explored different effect parametrizations, sample sizes, proportions of modifying to non-modifying variables, and number of confounding variables. For all analyses, we used 10-fold cross fitting, and linear projection approach to identify pre-specified modifiers. Our preliminary results suggest that both the causal forest and the DR learner have good 95% confidence interval coverage in most settings. However, the DR learner outperformed the causal forest in coverage (93% vs. 88%) under the scenarios of strong treatment effect but low heterogeneity. We also found that the best linear projections may not always reliably identify pre-specified effect modifiers when either method is used, especially in small sample sizes (with a successful identification of 53% at best scenario). This will provide practical insights to guide method selection for estimating CATEs in empirical research.

Day: Thursday, Board 18, Side B

Title: Causal machine learning for high-dimensional mediation analysis using interventional effects mapped to a target trial

Presenter: Tong Chen

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Coauthors: Stijn Vansteelandt, David Burgner, Toby Mansell, Margarita Moreno-Betancur

Abstract: Longitudinal cohort studies frequently analyse biological specimens, including blood, urine, and faeces, to obtain high-dimensional 'omics' and other biomarker data. These data contribute to understanding the multiple biological pathways mediating the effects of exposures on disease risk. Recent causal mediation analysis methodology using interventional

effects that map to a target trial offers a promising avenue for estimating indirect effects via multiple biomarkers. However, current implementations rely on parametric methods that may not be valid for high-dimensional problems where there will be many variables (multiple biomarkers) and complex relationships but a limited sample size. We study different versions of interventional effect estimands that map to a target trial and employ efficient influence functions within a nonparametric model to derive causal machine learning estimators. We then develop a targeted minimum loss-based estimator and a one-step estimator. The nuisance parameters of these estimators can be modelled using machine learning to tackle high-dimensional problems, with the use of sample splitting enabling valid inference. We show that these estimators are root-n consistent, efficient, and multiply robust. We examine the performance of these methods in simulation studies and apply them to investigate metabolomic pathways (represented by 75 metabolites measured by Nuclear Magnetic Resonance) linking obesity (binary exposure) and later blood pressure using data from the Longitudinal Study of Australian Children.

Day: Thursday, Board 19, Side A

Title: Causal Inference with semiparametric estimation for genomics: Detecting small effect sizes in large sample populations with weak unit dependence

Presenter: Sjoerd Beentjes

Affiliation: University of Edinburgh

Coauthors: Olivier Labayle, Kelsey Tetley-Campbell, Joshua Slaughter, Mark van der Laan, Chris Ponting, Ava Khamseh

Abstract: We present a unified statistical workflow for the semiparametric efficient and double robust estimation of causal n-point interactions amongst categorical variables in the presence of confounding and weak population dependence. N-point interactions, or Interaction ATEs (IATEs), are a direct generalisation of the usual average causal effect. We estimate IATEs with cross-validated and/or weighted versions of Targeted Minimum Loss-based Estimators (TMLE) and One-Step Estimators (OSE). The effect of dependence amongst units on variance estimates, is corrected by utilising sieve plateau variance estimators based on a meaningful notion of unit relatedness.Our motivating application is the targeted estimation of causal genetic effects on trait, including two-point and higher-order gene-gene and gene-environment interactions, in large-scale genomic databases such as UK Biobank and All of Us. Computing millions of estimates in large cohorts in which small effect sizes are expected, necessitates minimising model-misspecification bias to control false discoveries. We report on significant findings, both replicated and novel contradicting overconfident findings from restrictive linear mixed models commonly employed in statistical genomics, as well as differing finite-but-large sample performance between asymptotically equivalent OS and TML estimators.All cross-validated and/or

weighted TMLE and OSE for the IATE n-point interaction, as well as ATEs and CATEs and functions thereof, are implemented in the Julia package TMLE.jl for general purpose. For high-throughput applications in population genomics, we provide the open source Nextflow pipeline and software TarGene that integrates seamlessly with modern high-performance computing platforms.

Day: Thursday, Board 19, Side B

Title: Estimation of the Number Needed to Treat, the Number Needed to be Exposed, and the Exposure Impact Number with Instrumental Variables

Presenter: Valentin Vancak

Affiliation: Holon Institute of Technology

Coauthors: Arvid Sjölander

Abstract: The Number needed to treat (NNT) is an efficacy index defined as the average number of patients needed to treat to attain one additional treatment benefit. In observational studies, specifically in epidemiology, the adequacy of the populationwise NNT is questionable since the exposed group characteristics may substantially differ from the unexposed. To address this issue, groupwise efficacy indices were defined: the Exposure Impact Number (EIN) for the exposed group and the Number Needed to be Exposed (NNE) for the unexposed. Each defined index answers a unique research question since it targets a unique sub-population. In observational studies, the group allocation is typically affected by confounders that might be unmeasured. The available estimation methods that rely either on randomization or the sufficiency of the measured covariates for confounding control will result in inconsistent estimators of the true NNT (EIN, NNE) in such settings. Using Rubin's potential outcomes framework, we explicitly define the NNT and its derived indices as causal contrasts. Next, we introduce a novel method that uses instrumental variables to estimate the three aforementioned indices in observational studies. We present two analytical examples and a corresponding simulation study. The simulation study illustrates that the novel estimators are consistent, unlike the previously available methods, and their confidence intervals meet the nominal coverage rates. Finally, a real-world data example of the effect of vitamin D deficiency on the mortality rate is presented.