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Personalized Recommendations for Neurodegenerative Disease

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Public deliverable report

D3.18: Publication of a causality study based on an instrumental variables approach

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1. Introduction

Mediation analysis breaks down the causal effect of a treatment on an outcome into an indirect effect, acting through a third group of variables called mediators and a direct effect, operating through other mechanisms. We provide a thorough evaluation of estimators for direct and indirect effects in the context of causal mediation analysis for binary, continuous and multi-dimensional mediators. We consider standard parametric implementations of classical estimators, and propose and assess the relevance of several extensions inspired from double or debiased machine learning, in particular non-parametric models, regularization, probability calibration and cross-fitting. Our results show that most methods obtain reasonable estimates under model misspecification, but some methods, including multiply-robust methods, are very sensitive to (near-)violations of the overlap assumption. This trend is even more pronounced in multi-dimensional settings. We also describe settings where the use of more complex non-parametric models for estimation is relevant.

To illustrate the considered methods on real data, we examine the causal path from higher education graduation to middle-age general intelligence in the UK Biobank, which includes several potential binary, continuous and multi-dimensional mediators. This analysis shows that this effect is partially mediated by having a physical occupation, and brain characteristics measured through MRI, but not by the brain age, a popular MRI-derived phenotype.

2. Partners involved

Inria is involved.

3. Description of work performed

In this work, we focus on the problem of estimating the direct and indirect effects of one or several mediators jointly (no path-specific effect) using classical approaches, or more recent approaches that are robust to model misspecification. We propose new variants of existing estimators, with more flexible machine learning models to account for complex relations between the variables of interest. We provide a comprehensive evaluation of classical and more recent methods on simulated data, extending the work of 28 for a binary mediator to the continuous and multi-dimensional mediators. We rely on a diversity of simulation settings to explore the practical implications of violations of parametric model specifications, violations to the overlap assumption, variations in the number of observations, and choice of the confounder and mediator variables. This benchmark provides a good overview of available estimators, their validity conditions and limitations which constitutes a valuable guide to the practitioner.

To go beyond performance analysis on simulated data, we conduct several mediation analyses on real data from the UK Biobank to explore cognitive functions in a cohort of middle-aged adults. UK Biobank is a prospective cohort of about 500,000 healthy participants in the UK with very thorough socio-demographic, medical, lifestyle, physical and cognitive assessment.

A subset of nearly 40,000 participants also underwent a more enhanced functional exploration including brain structural and functional magnetic resonance Imaging (MRI). This unprecedentedly large imaging database allows us to assess potential role of the brain structure in the shaping of cognitive functions, while observing potential confounders. The results obtained for several potential mediators of different nature (binary, continuous and multidimensional) further illustrate the properties of the different considered estimators.

4. Results

We have applied the seven mediation estimators (with a total of 34 variants) considered in this study on a variety of simulated datasets with varying types of mediator, and degree of non-linearity of the outcome and mediator models. We compare the relative error for the total, direct and indirect effect.

The total effect is almost always well estimated, but not the direct and indirect effects that exhibit opposite errors. For the simplest simulations with a one-dimensional binary mediator, the different estimators behave as expected. All estimators achieve a very small or even negligible error in the "linear" setting where all models are well specified. The misspecification of the mediator model induces an error in the IPW estimator that relies solely on the estimation of the propensity of the treatment given the covariates, and on the propensity of the treatment given the covariates and the mediator; estimation of the latter can be impaired by the introduction of the interaction between the covariates and the mediator. The misspecification of the outcome model leads to a high estimation error for the estimators that rely the most on regression approaches of the outcome given the treatment, covariates and mediator, namely the coefficient product, the G-computation, the simulation based and the G-estimator estimators.

Interestingly, estimators that require both the mediator and the outcome models to be correctly specified are more robust to a misspecification of the mediator model. This might be due to our simulation setting where the binary mediator has a more modest range of possible error, while the outcome is a continuous variable. The multiply robust estimator and the double maching learning estimator have no error in that case, which illustrates their theoretical robustness property. Finally, when both the mediator and the outcome model are misspecified, all estimators exhibit an erroneous estimation of the direct and indirect effects, except the two multiply robust estimators.

We observe a similar pattern for the results with a continuous one-dimension mediator. In that setting, only the coefficient product, the IPW and the double-machine-learning mestimator provide a result. All estimators have a very small or no error when all models are linear; misspecification of the mediator but not the outcome model leads to an error for the IPW estimator, and the opposite for the coefficient product. The double machine learning estimator is robust to misspecification, even of both models.

Finally, for a continuous multi-dimension mediator, we additionaly observe that the double machine learning approach is no-longer robust to a misspecification of the outcome model.

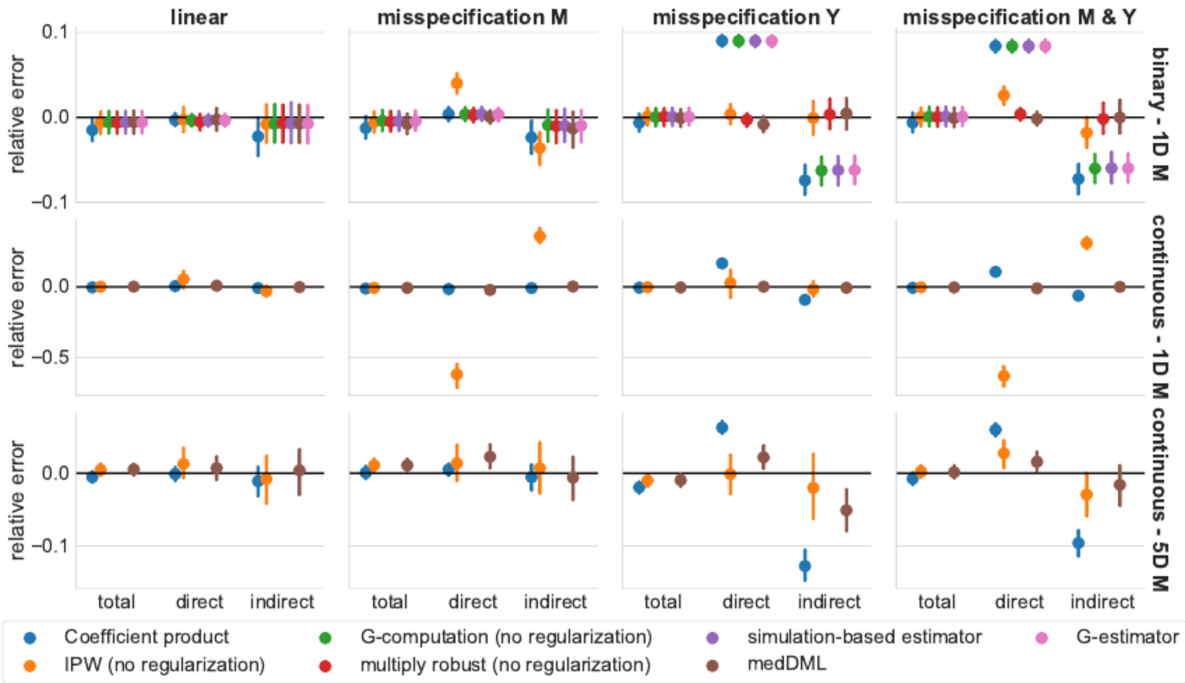

Figure 1: Total and natural direct and indirect effects. We show results for four scenarii of generative model specification, violating or not the parametric linear nuisance models of some estimators. Each column corresponds to a distinct specification of simulated models. The rows correspond to different mediator types, labeled on the right. Each dot represents the average relative error over 50 repetitions, and the error bars are bootstrap 95% confidence intervals. All simulations are in the "high mediated proportion without overlap violation" framework with n = 1, 000 observations. Most estimators only handle binary one-dimensional mediators, and have no results for the second and third rows. The total effect is generally well estimated in all situations, but not the direct and indirect effects. The indirect and direct effects can be different, leading to a lack of symmetry in their relative error values, even if their absolute values are equal, leading to no error for the total effect estimation. Model misspecifications engender estimation errors for most estimators, especially when the outocome model is misspecified.

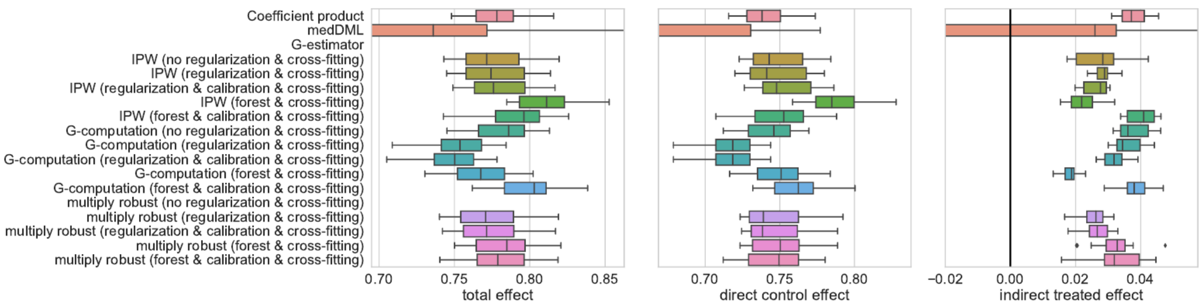

Figure 2: Mediation analysis of a physical job, for the effect on education on cognitive functions. The total, natural direct and indirect effects are shown in the panels from left to right. The scale was adjusted to show most results in details, so that the boxplots of the medDML and multiply robust (without regularization) estimators are cropped. The G-estimator method failed on this dataset. With the exception of medDML, G-estimator and the unregularized multiply robust estimator implementation, all estimators similar results for the total, direct and indirect effect, with a small but non-null indirect effect of a physical job.

5. Conclusion, next steps

This study highlights a number of potential research directions, in particular for estimators able to handle continuous or multi-dimensional mediators. As of now, only the coefficient product has satisfactory performances in most settings. A first line of work consists in increasing the stability of inverse-propensity based methods, with several solutions proposed outside of the mediation field . Some clarification is also needed on how to best leverage more complex machine learning approaches to better estimate causal quantities.

Our implementations are available as a Python package at https://github.com/

judithabk6/med_bench.