Causal mediation analysis in presence of multiple mediators uncausally related

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Résumé. L'analyse de médiation vise à démêler les effets d'un traitement sur une variable de sortie par le biais de mécanismes de causalité alternatifs et est devenue une pratique courante dans les applications biomédicales et en sciences sociales. Le cadre causal basé sur les contrefactuels est actuellement l'approche standard de la médiation, avec d'importants progrès méthodologiques introduits dans la littérature au cours de la dernière décennie, en particulier pour la médiation simple, c'est-à-dire avec un médiateur à la fois. Parmi une variété d'approches alternatives, K. Imai et al. ont montré des résultats théoriques et développé un package `R` pour traiter la médiation simple ainsi que la médiation multiple impliquant plusieurs médiateurs indépendants conditionnellement au traitement et aux covariables. Cette approche ne permet pas de considérer la situation souvent rencontrée dans laquelle une cause commune non observée induit une corrélation fallacieuse entre les médiateurs. Dans ce contexte, que nous qualifions de médiation avec des médiateurs liés de manière non-causale, nous montrons que, sous de nouvelles hypothèses appropriées, les effets naturels directs et indirects sont identifiables de manière non paramétrique. Ces résultats sont rapidement traduits en estimateurs non biaisés utilisant le même algorithme quasi-bayésien mis au point par Imai et al que nous avons adapté au cas multiple. Nous validons notre méthode par une étude de simulation originale. À titre d'illustration, nous appliquons notre méthode sur un ensemble de données réelles d'une grande cohorte afin d'évaluer l'effet du traitement hormonal sur le risque de cancer du sein par l'intermédiaire de trois médiateurs, à savoir les zones mammaires denses, les zones mammaires non denses et l'indice de masse corporelle.

Mots-clés. Biostatistique, Mèdecine, épidmiologie, Analyse causale, Analyse de médiation, Effets direct et indirect, Médiateurs Indépendants, Médiateurs Corrélés, Simulation de contrefactuel

Abstract. Mediation analysis aims at disentangling the effects of a treatment on an outcome through alternative causal mechanisms and has become a popular practice in biomedical and social science applications. The causal framework based on counterfactuals is currently the standard approach to mediation, with important methodological advances introduced in the literature in the last decade, especially for simple mediation, that is with one mediator at the time. Among a variety of alternative approaches, K. Imai et al. showed theoretical results and developed an `R` package to deal with simple mediation as well as with multiple mediation involving multiple mediators conditionally independent given the treatment and baseline covariates. This approach does not allow to consider the often encountered situation in which an unobserved common cause induces a spurious correlation between the mediators. In this context, which we refer to as mediation with uncausally related mediators, we show that, under appropriate hypothesis, the natural direct and indirect effects are non-parametrically identifiable. These results are promptly translated into unbiased estimators using the same quasi-Bayesian algorithm developed by Imai et al. We validate our method by an original simulation study. As an illustration, we apply our method on a real data set from a large cohort to assess the effect of hormone replacement treatment on breast cancer risk through three mediators, namely dense mammographic area, nondense area and body mass index.

Keywords. Biostatistics, Medicine, epidemiology, Causal analysis, Correlated mediators, Direct and indirect effects, Independent mediators, Mediation analysis, Simulation of counterfactuals

1 Context and summary of our results

1.1 Mediation Analysis

Causal mediation analysis comprises statistical methods to study the mechanisms underlying the relationships between a cause, an outcome and a set of intermediate variables. This approach has become increasingly popular in various domains such as biostatistics, epidemiology and social sciences. Mediation analysis applies to the situation depicted by the causal directed acyclic graph of Figure 1, where an exposure (or treatment) T affects an outcome Y either directly or through one or more intermediate variables referred to as *mediators*. The aim of the analysis is to assess the total causal effect of T on Y by decomposing it into a *direct* effect and an *indirect* effect throug the mediator(s).

Mediation analysis originally developed within the setting of linear structural equation modeling (LSEM) [[Baron and Kenny, 1986, James et al., 1982, MacKinnon, 2008]]. Following the seminal works by [Robins and Greenland, 1992] and [Pearl, 2001], a formal framework based on counterfactual established itself as the standard approach to mediation analysis, with a growing methodological literature, see for instance [[Petersen et al., 2006, VanderWeele and Vansteelandt, 2009, VanderWeele and Vansteelandt, 2010, Lange et al., 2012]] and the comprehensive book by [VanderWeele, 2015].

In this work, we adopt the point of view and formalism of [Imai et al., 2010a, Imai et al., 2010b], who put forward a general approach based on counterfactuals to define, identify and es-

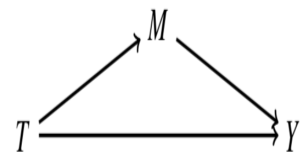

Figure 1: Simple mediation model with one mediator M and no confounding covariates.

timate causal mediation effects without assuming any specific statistical model in the particular case of a single mediator. Their theoretical results are based on a strong set of assumptions known as *Sequential Ignorability.* These conditions are interpreted as the requirement that there must be no confounding of the $T-Y$, $T-M$ and $M-Y$ relationships after adjustment on the measured pretreatment covariates (i.e. cofounder that is not affected by T) and T, and moreover that there must not be posttreatment confounding (i.e. cofounder that is affected by T) between M and Y whatsoever, measured or unmeasured. In particular, [Imai et al., 2010b, Imai et al., 2010a] proved that under Sequential Ignorability, the average indirect effect is non parametrically identified, see Theorem **??** in the next section, and proposed a sensitivity analysis to assess the robustness of estimates to violations of Sequential Ignorability. Moreover they introduced estimation algorithms for the effects of interest that are implemented in the widely used `mediation` R package [[Tingley et al., 2014]].

1.2 Mediation Analysis with Multiple Mediators

When multiple mediators are involved in the mediation model, three cases may arise, as shown in Figure 2: in Fig. 2(a) mediators are conditionally independent given the treatment and measured covariates (not depicted here), in Fig. 2(b) mediators are causally ordered, that is one affects the other; in Fig. 2(c) mediators are conditionally dependent given the treatment and measured covariates without being causally ordered. In the latter situation, we will talk about *uncausally correlated* mediators as opposed to the situation of Fig. 2(b) where mediators are causally correlated. We will also refer to the cases depicted in figures 2(a) and 2(c) as mediation with multiple *causally unrelated* mediators.

Although the models in figures 2(a) and 2(b) have been treated in the last few years, [[VanderWeele and Vansteelandt, 2014, Lange et al., 2014, Daniel et al., 2015]], to the best of our knowledge the situation of uncausally correlated mediators of Fig. 2(c) has never been fully addressed, and this despite the fact that it is often encountered in practice where it is seldom possible to control for all possible covariates inducing spurious correlation between mediators. The aim of this work is to introduce results on non-parametric identifiability in this situation, building on the works of K. Imai et al.

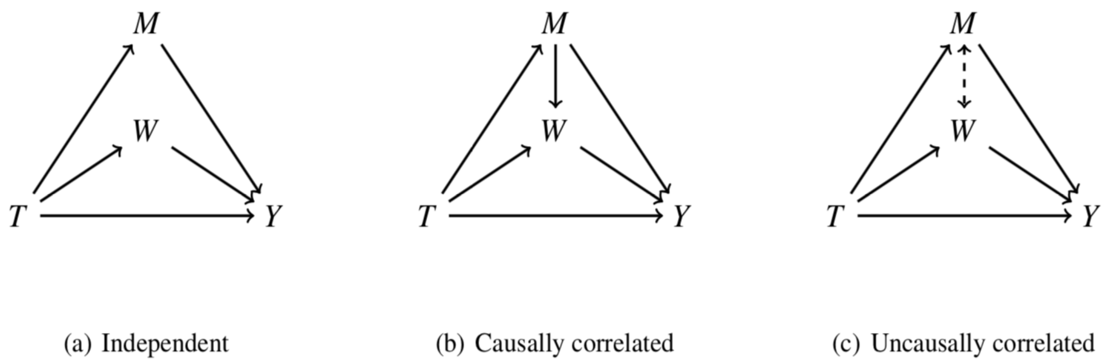

Figure 2: Three situations with multiple mediators M and W.

[Imai and Yamamoto, 2013] extended the above mentioned results of non parametric identifiability to the situation of causally unrelated mediators. To that end, they started by introducing definitions for the different effects of interest in the case of multiple mediators. When mediators are causally unrelated, and Sequential Ignorability holds, they suggested to process several single mediator analysis in parallel, one mediator at the time. Obviously, this approach leads to a biased estimate of the direct effect, because it forces the indirect effects via all other mediators to contribute to the direct effect. More subtlety, this approach is not appropriate when mediators are uncausally correlated due to an unmeasured covariate U causally affecting both mediators M and W as in Figure 3. As a matter of fact, in this situation U is an unobserved confounder of the relationship between M and Y and Sequential Ignorability does not hold. This key fact was remarked by [Imai and Yamamoto, 2013] and [VanderWeele and Vansteelandt, 2014], but no explicit solution to the problem was proposed other then conducting the above mentioned sensitivity analysis.

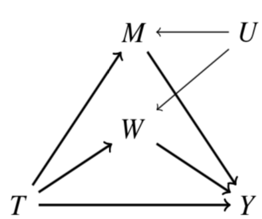

Figure 3: Correlation between mediators due to U.

1.3 Our original contribution

In this work, we focus on the scenario of multiple causally unrelated mediators (either independent, Fig. 2(a), or uncausally correlated, 2(c)). Firstly, we extend the theoretical results developed by K. Imai and coauthors to this scenario, by showing that under assumptions alternative to Sequential Ignorability, the effects of interest are identifiable. In particular, if these new assumptions hold, it is possible to have unbiased estimation of the direct, indirect and joint indirect effect, even in presence of uncausally correlated mediators. We give formulas for estimating the effects of interest for both continuous and binary outcomes. Secondly, we implement the estimation algorithms in R; a documented R package is under preparation and will be soon posted on GitHub. Thirdly, we conduct a simulation study showing that our methods result in unbiased estimates of the direct and indirect effects. To this aim, we suggest an original method based on the generation of large datasets of counterfactuals from causal structural models. These data are then used to both compute the true direct and indirect effects and to extract observational data on which methods can be tested. At last, we apply our method to a real dataset from a large cohort to assess the effect of hormone replacement treatment on breast cancer risk through three uncausally correlated mediators, namely dense mammographic area, nondense area and body mass index.

All the details can be found in a preprint [Jerolon et al., 2018]. This work is under submission.

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