Identifying Direct Causal Effects Under Unmeasured Confounding

Philippe Boileau*[1], Nima S. Hejazi*[2], Ivana Malenica*[1], Sandrine Dudoit[1], Mark J. van der Laan[1]

[1]University of California, Berkeley; [2]Weill Cornell Medicine

Introduction & Motivations

- Developing *mechanistic* understandings of causal effects is a ubiquitous goal across scientific disciplines.
- The natural direct and indirect effects are common target causal parameters since they are nonparametrically identified.
- Identification assumes absence of unmeasured confounders of exposure–mediator, mediator–outcome, and exposure–outcome pathways — but this is *not* completely necessary.
- The natural direct and indirect effects arise from a decomposition of the average treatment effect (ATE), and the
  - natural indirect effect (NIE) captures the portion of the ATE passing through the mediators (Z), while the
  - natural direct effect (NDE) captures the remainder of the ATE, through all paths excluding Z.

The Statistical Problem

Consider cohort data collected through time as $O = (W, A, Z, Y)$. O does not include V, though the complete data X does.

Let $O \sim P_0 \in \mathcal{M}$, with $\mathcal{M}$ being the nonparametric *statistical model*. Likelihood of the observed data under $\mathcal{M}$ is:

$$p(o) = \prod_{i=1}^{n} q_Y(y_i \mid w_i, a_i, z_i) q_Z(z_i \mid w_i, a_i) g_A(a_i \mid w_i) q_W(w_i).$$

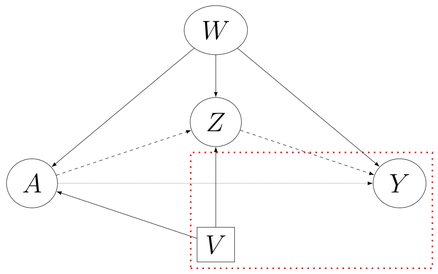
The average treatment effect may be decomposed as

$$\begin{aligned}\Psi^F_{\text{ATE}}(P_{U,X,0}) = &\underbrace{\mathbb{E}_{U,X,0}[Y(1, Z(1)) - Y(1, Z(0))]}_{\text{NIE}} \\ &+ \underbrace{\mathbb{E}_{U,X,0}[Y(1, Z(0)) - Y(0, Z(0))]}_{\text{NDE}},\end{aligned}$$

where $Y(1, Z(0))$ arises from a *joint* intervention on treatment and mediators (Z), setting them to incompatible values. The NDE is

$$\begin{aligned}\Psi^F_{\text{NDE}}(P_{U,X,0}) = \int_{\mathcal{W},\mathcal{Z}} &\mathbb{E}[Y(1, z) - Y(0, z) \mid W = w] \\ &p_Z(z \mid A = 0, w) p_W(w) \, d\mu(z) \, d\nu(w) \, .\end{aligned}$$

Causal Identification



(A1) No unmeasured endogenous pathways:
$f_Y(Z, A, W, V, U_Y) \equiv f_Y(Z, A, W, U_Y)$.

(A2) Conditional expectation equivalence:
$\mathbb{E}(Y \mid Z, A = 1, W, V) \equiv \mathbb{E}(Y \mid Z, A = 1, W)$

Theorem

Under assumptions A1 and A2, $\Psi^F_{\text{NDE}}(P_{U,X,0})$ is identified by

$$\begin{aligned}\Psi(P_0) = \mathbb{E}_{P_0}\mathbb{E}_{P_0}\{&\mathbb{E}_{P_0}(Y \mid W, A = 1, Z) \\ &- \mathbb{E}_{P_0}(Y \mid W, A = 0, Z) \mid A = 0, W\} \, .\end{aligned}$$

Inference

Existing estimation and testing approaches are compatible with this relaxed identification strategy. For example,

- targeted maximum likelihood estimator of Zheng and van der Laan [2012]
- one-step bias-corrected estimator based on the efficient influence function of Tchetgen Tchetgen and Shpitser [2011].

Both estimators are *multiple-robust*, *asymptotically linear* under fairly non-restrictive assumptions, and compatible with cross-fitting. Both estimators are implemented in the `medoutcon` `R` package.

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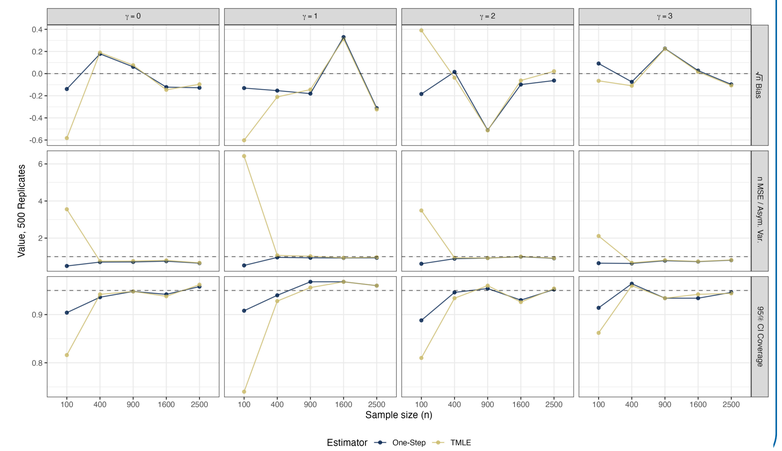
Numerical Experiments

We consider the following data-generating process:

$$\begin{aligned}W_1 &\sim \text{Unif}(-1, 1);\ W_2, V \sim \text{Norm}(0, 1) \\ A|W, V &\sim \text{Bern}\left((1 + \exp\{-W_1 - W_2 - V\})^{-1}\right) \\ Z|A, W, V &\sim \text{Bern}\left((1 + \exp\{-W_1 - W_2 - \gamma V - 3A\})^{-1}\right) \\ Y|Z, A, W, V &\sim \text{Norm}(3A + W_1 + W_2 + Z, 1) \, .\end{aligned}$$



Conclusions

- The NDE is identifiable under unmeasured exposure–mediator confounding by a *well-studied* statistical functional!
- The NDE has recently been used to study the *proportion of vaccine effect mediated* through candidate immune correlates.
  - Our results strengthen "out-of-the-box" uses of the NDE.
  - Exposure–mediator confounders in vaccine studies: prior infection history, immunocompromised status, genetics.

References

Wenjing Zheng and Mark J. van der Laan. Targeted maximum likelihood estimation of natural direct effects. *The International Journal of Biostatistics*, 8(1):1–40, 2012. doi: doi:10.2202/1557-4679.1361. URL `https://doi.org/10.2202/1557-4679.1361`.

Eric J Tchetgen Tchetgen and Ilya Shpitser. Semiparametric estimation of models for natural direct and indirect effects. Working Paper 129, Harvard University, 2011. URL `https://biostats.bepress.com/harvardbiostat/paper129/`.

* *indicates shared first-authorship, ordered alphabetically.*