



IDENTIFYING DIRECT CAUSAL EFFECTS UNDER UNMEASURED CONFOUNDING

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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 — both identifiable without structural assumptions.
- 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), defined by a
 - *joint* intervention on exposure (A) and mediators (Z), where
 - natural indirect effect (NIE) captures the portion of the ATE that passes only through the mediators, while the
 - natural direct effect (NDE) captures the remainder of the ATE, that is, through all paths excluding Z .

The Statistical Problem

Full (unobserved) data is $X = (W, V, A, Z, Y)$, and we observe $O = (W, A, Z, Y)$. Exposure–mediator confounder V **not** part of O .

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

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

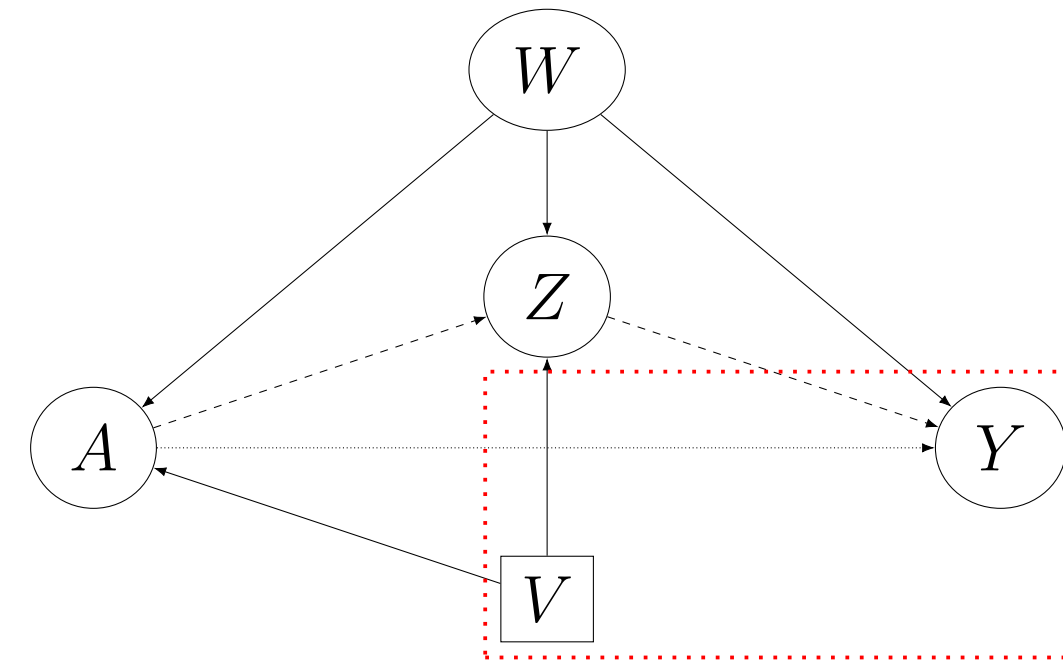
The average treatment effect may be decomposed as

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

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

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

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:

$$\mathbb{E}(Y | Z, A = 1, W, V) \equiv \mathbb{E}(Y | Z, A = 1, W)$$

Theorem

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

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

Estimation & Inference

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

- targeted maximum likelihood estimator of Zheng and van der Laan [2012], or the
- one-step estimator of Tchetgen Tchetgen and Shpitser [2011].

Both estimators are *multiple-robust* (by being based on the efficient influence function), *asymptotically linear* under fairly non-restrictive assumptions, compatible with *cross-fitting* of nuisance estimators.

Both estimators are implemented in the **medoutcon** R package (check it out at <https://github.com/nhejazi/medoutcon>).

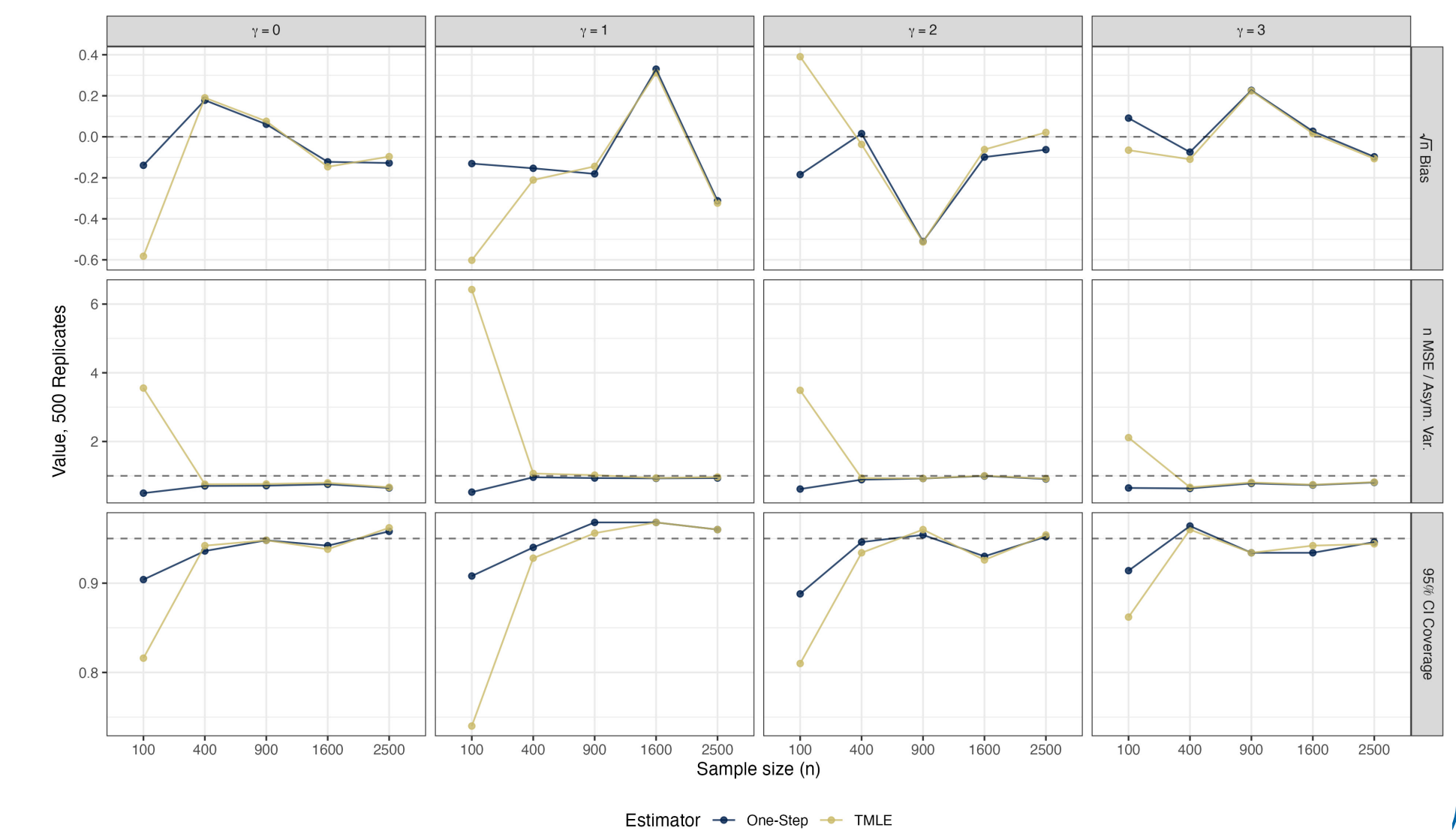
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Numerical Experiments

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

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