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Robust inference on indirect causal effects

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Background & Motivation

- The natural indirect effect (NIE) has emerged as the most common form of causal indirect effect in the mediation literature
- In the following settings, the NIE may be unsatisfactory:

1. If the exposure of interest is harmful (i.e. HIV status), then the NIE requires conceiving of an intervention that would force a person to become HIV positive
2. In the presence of exposure-outcome confounding, the NIE is not nonparametrically identified

- To address both of these challenges, we propose a new form of indirect effect, the population intervention indirect effect (PIIE)

Notation & Assumptions

Setting: exposure *A*, mediator(s) *Z*, outcome *Y*, and set of measured confounders *C*

Notation:

$Z(a^*)$ counterfactual mediator had exposure taken level *a**

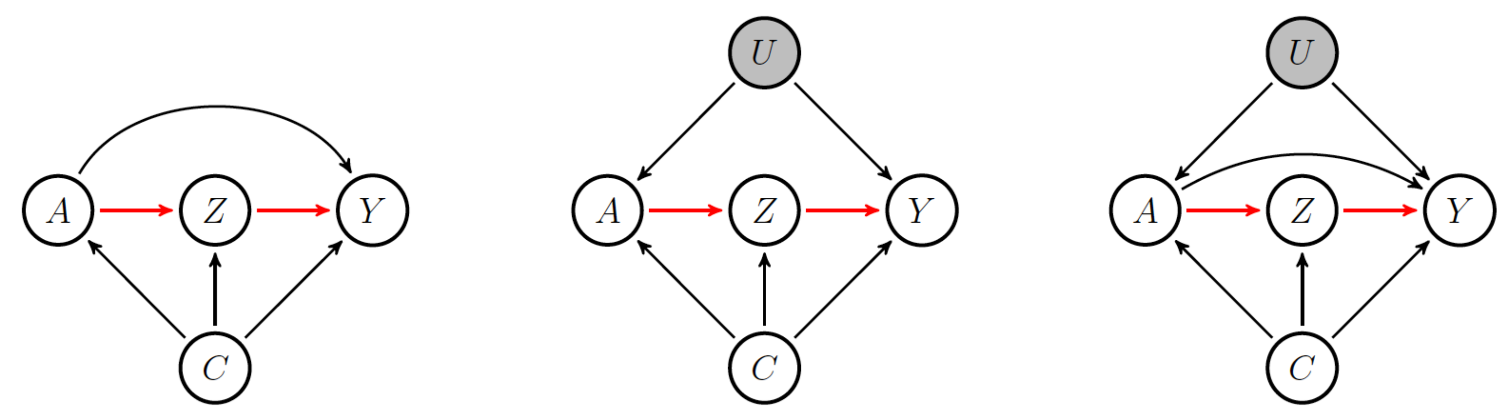
$Y(Z(a^*))$ counterfactual outcome had exposure taken its natural level and the mediator variable taken the value it would have under *a**

$PIIE(a^*) = E[Y - Y(Z(a^*))]$ the contrast between the observed outcome mean for the population and the population had the mediator taken the value it would have under *a**

Assumptions:

M1. Consistency assumptions:
(1) If $A = a$, then $Z(a) = Z$,
(2) If $A = a$, then $Y(a) = Y$,
(3) If $A = a$ and $Z = z$, then $Y(a, z) = Y$
M2. $Z(a^*) \perp A \mid C = c \quad \forall\, a^*, c$
M3. $Y(a, z) \perp Z(a^*) \mid A = a, C = c \quad \forall\, z, a, a^*, c$
M4. $Y(a, z) \perp Z \mid A = a, C = c \quad \forall\, z, a, c$
M5. $Y(a, z) \perp A \mid C = c \quad \forall\, z, a, c$

Figure 1. Causal graphs. The indirect effects in red are identified under an NPSEM-IE (Pearl, 2009) interpretation of the graph.



(a) classic mediation NIE and PIIE | (b) front-door NIE and PIIE | (c) proposed PIIE only

Nonparametric Identification

Under assumptions **M1-4**, or **Figure 1c**, the population intervention indirect effect is given by,

$$PIIE(a^*) = E[Y] - E[Y(Z(a^*))] = E[Y] - \Psi$$

where

$$\Psi = \sum_{z,c} Pr(Z = z | A = a^*, C = c) \times \sum_{a} E(Y | A = a, Z = z, C = c) Pr(A = a | C = c) Pr(C = c)$$

Estimation & Inference

- We propose parametric and semiparametric estimators of Ψ, and thus the PIIE, given in **Table 1** (*formulae omitted*)
- The estimators are consistent and asymptotically normal under their assumed semiparametric model

Table 1. Proposed estimators for PIIE

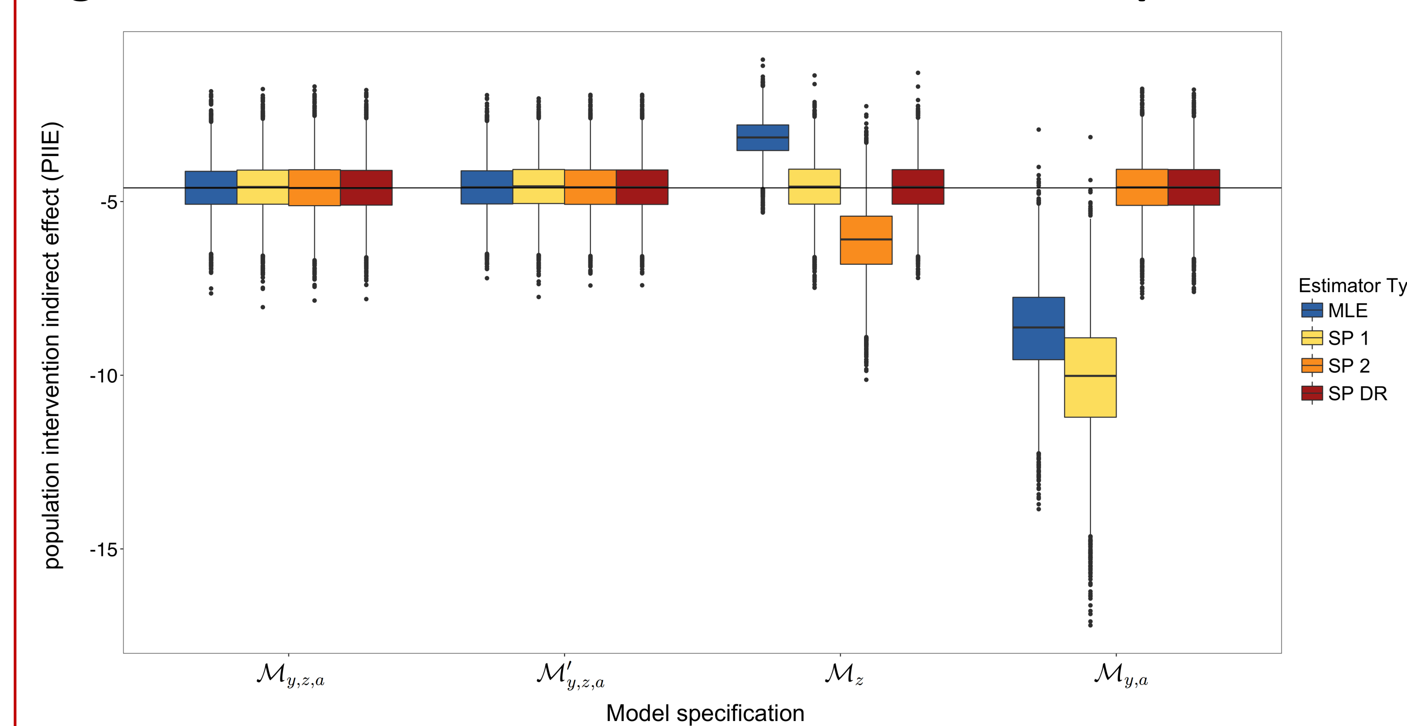
Estimator	Correct model specification	
Parametric (*MLE*)	$\mathcal{M}_{y,z,a}$	Exposure, mediator, and outcome
Semiparametric (*SP1*)	$\mathcal{M}_{z}$	Mediator only
Semiparametric (*SP2*)	$\mathcal{M}_{y,a}$	Exposure and outcome
Semiparametric Doubly-Robust (*DR*)	$\mathcal{M}_{union}$	Mediator **or** both exposure and outcome

Simulation Study

Goal: To assess the performance of the parametric and semiparametric estimators in the presence of:
(i) exposure-outcome unmeasured confounding ($\mathcal{M}'_{y,z,a}$)
(ii) model misspecification (scenarios $\mathcal{M}_z$ & $\mathcal{M}_{y,a}$)

Data Generation: Binary exposure A, continuous mediator Z (depends on A), and continuous outcome Y (depends on A,Z,AZ). Additionally, three binary confounders C: one for the A-Z relationship and two for A-Z-Y relationship are included

Figure 2. Simulation results under various model specifications



Important Connections to Prior Literature

- In contrast to the PIIE, the NIE needs the additional assumption **M5** (no exposure-outcome confounding) for identification (**Figure 1a**)
- The above expression for Ψ is closely connected to **Judea Pearl's front-door** formula. If there is full mediation by *Z*, then Ψ gives the front-door formula (**Figure 1b**)
- The PIIE is in fact the indirect component of the **population intervention effect** (Hubbard and Van der Laan, 2008)

References & Funding Information

[1] Hubbard, A. E., & Van Der Laan, M. J. (2008). Population intervention models in causal inference. Biometrika, 95(1), 35-47.
[2] Pearl, J. (2009). Causality. Cambridge University Press.

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