Uncovering Causal Mechanisms: Mediation Analysis and Surrogate Indices

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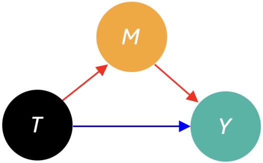
Mediation Analysis: Identifying Mechanisms Underlying Treatment Effects on Primary Outcomes

Part I. Introduction to Mediation

Causal Mechanism as Direct and Indirect Effects

- Directed Acyclic Graph (DAG; Pearl, 2000)
  - $T \in \mathcal{T} = \{0, 1\}$: treatment
  - $M \in \mathcal{M}$: mediator (mechanism variable)
  - $Y \in \mathcal{Y}$: observed outcome



- Direct effect: Effect of T on Y while holding M constant
- Indirect effect: Effect of T on Y through M

- DAG = Nonparametric Structural Equation Model (NPSEM)

$$Y = f_Y(M, T, \epsilon)$$
$$M = f_M(T, \eta)$$

where ϵ and η are i.i.d. and are usually omitted from DAG

Controlled Direct Effect (CDE)

- $Y(t, m) \in \mathcal{Y}$: potential outcome when $T = t$ and $M = m$
- Definition

$$\begin{aligned} \text{Individual:} \quad \text{CDE}_i(m) &:= Y_i(1, m) - Y_i(0, m) \\ \text{Average:} \quad \overline{\text{CDE}}(m) &:= \mathbb{E}[Y(1, m) - Y(0, m)] \end{aligned}$$

  for a given mediator value $m \in \mathcal{M}$

- Interpretation
  - direct effect of treatment while holding the mediator constant at m
  - effect of joint intervention on T and M

- If M fully captures treatment effect, CDEs will be zero for all m
- Potential interaction effects:

$$\text{CDE}_i(m) \neq \text{CDE}_i(m') \quad \text{for some } i \text{ and } m \neq m'$$

Natural Indirect Effect (NIE)

- Definition (Robins and Greenland, 1992; Pearl, 2001)

$$\text{Individual:} \quad \text{NIE}_i(t) \;:=\; Y_i(t, M_i(1)) - Y_i(t, M_i(0))$$
$$\text{Average:} \quad \overline{\text{NIE}}(t) \;:=\; \mathbb{E}[Y(t, M(1)) - Y(t, M(0))]$$

- Interpretation
  - effect of change in M on Y induced by T
  - change M from $M(0)$ to $M(1)$ while holding T at $t = 0$ or $t = 1$
  - zero treatment effect on M implies zero NIE

- Represents the causal effect of T on Y through M
- Complete mediation $\rightsquigarrow$ $\text{NIE}_i = \text{TE}_i := Y_i(1, M_i(1)) - Y_i(0, M_i(0))$

Treatment Effect Decomposition

- Natural direct effect (NDE):

$$\begin{aligned} \text{Indiviual:} \quad \text{NDE}_i(t) &:= Y_i(1, M_i(t)) - Y_i(0, M_i(t)) \\ \text{Average:} \quad \overline{\text{NDE}}(t) &:= \mathbb{E}[Y(1, M(t)) - Y(0, M(t))] \end{aligned}$$

  - change T from 0 to 1 while holding M constant at $M(t)$
  - causal effect of T on Y, holding M constant at its potential value that would be realized when $T = t$
- Represents all mechanisms other than through M
  - Complete mediation $\rightsquigarrow$ $\text{NDE}_i(t) = 0$
  - No mediation $\rightsquigarrow$ $\text{NDE}_i = \text{TE}_i$
- Effect decomposition:

$$\begin{aligned} \underbrace{Y_i(1, M_i(1)) - Y_i(0, M_i(0))}_{=\text{total effect } (\text{TE}_i)} &= \text{NIE}_i(t) + \text{NDE}_i(1-t) \\ &= \frac{1}{2}\sum_{t=0}^{1}\{\text{NIE}_i(t) + \text{NDE}_i(t)\} \end{aligned}$$

Gender Bias and Educational Attainment (Chen et al. 2019)

- Data on Taiwanese families
  - Y: educational attainment of the oldest child who is female
  - T: gender of the second oldest child
  - M: number of siblings

- Gender bias
  - Direct effect: having a brother takes away resources from a female child
  - Indirect effect: having a brother leads to a smaller number of siblings and hence more resources
  - Direct and indirect effects may have opposite signs

- Causal effects of interest
  - CDE: effect of having a brother while keeping sibling size constant at a fixed value, e.g., 2
  - NDE: effect of having a brother while keeping sibling size constant at a value that would result, e.g., if the second child were male
  - NIE: effect of having a brother through sibling size

Take-aways I

- Causal mechanism
  - how and why (not just whether) treatment affects outcome
  - understanding of causal structure (DAG $=$ NPSEM)

- Causal quantities of interest
  - Controlled direct effect (CDE)
  - Natural direct and indirect effects (NDE, NIE)
  - Effect decomposition: $\text{TE} = \text{NDE} + \text{NIE}$
  - No similar decomposition for CDE
  - Complete mediation: $\text{CDE} = \text{NDE} = 0$ and $\text{NIE} = \text{TE}$
  - No mediation: $\text{NIE} = 0$ and $\text{NDE} = \text{TE}$

Part II. Mediation Analysis Under Pretreatment Confounding

Linear Structural Equation Model (LSEM)

- Let's build some intuition with LSEM
- Homogeneous effects without interaction:

$$
\begin{aligned}
Y_i &= \alpha_Y + \beta_Y T_i + \gamma_Y M_i + \epsilon_i \\
M_i &= \alpha_M + \beta_M T_i + \eta_i
\end{aligned}
$$

  - $\overline{\text{CDE}}(m) = \overline{\text{NDE}}(t) = \beta_Y$ for any m and t
  - $\overline{\text{NIE}}(t) = \beta_M \times \gamma_Y$ for any t
  - CDE and NDE are identical

- Homogeneous effects with interaction:

$$
Y_i = \alpha_Y + \beta_Y T_i + \gamma_Y M_i + \delta_Y T_i M_i + \epsilon_i
$$

  - $\overline{\text{CDE}}(m) = \beta_Y + m\delta_Y$
  - $\overline{\text{NDE}}(t) = \beta_Y + \delta_Y(\alpha_M + t\beta_M)$
  - $\overline{\text{NIE}}(t) = \beta_M \times \gamma_Y + t\beta_M \times \delta_Y$
  - CDE is different from NDE

LSEM with Heterogeneous Effects and Interaction

- Model

$$Y_i = \alpha_Y + \beta_Y^{(i)} T_i + \gamma_Y^{(i)} M_i + \delta_Y^{(i)} T_i M_i + \epsilon_i$$
$$M_i = \alpha_M + \beta_M^{(i)} T_i + \eta_i$$

  - $\overline{\text{CDE}}(m) = \bar{\beta}_Y + m\bar{\delta}_Y$ where $\bar{\beta}_Y = \mathbb{E}[\beta_Y^{(i)}]$ and $\bar{\delta}_Y = \mathbb{E}[\delta_Y^{(i)}]$
  - $\overline{\text{NDE}}(t) = \bar{\beta}_Y + \alpha_M \times \bar{\delta}_Y + \mathbb{E}[\delta_Y^{(i)}(t\beta_M^{(i)} + \eta_i)]$
  - $\overline{\text{NIE}}(t) = \mathbb{E}[\beta_M^{(i)} \times (\gamma_Y^{(i)} + t\delta_Y^{(i)})]$

- Heterogeneous effects may be correlated with one another
  - For example, $\mathbb{E}[\beta_M^{(i)} \times \gamma_Y^{(i)}] \neq \bar{\beta}_M \times \bar{\gamma}_Y$
  - Possible to have $\bar{\beta}_M, \bar{\gamma}_Y > 0$ but $\mathbb{E}[\beta_M^{(i)} \times \gamma_Y^{(i)}] < 0$ or vice versa

- $\bar{\beta}_M$, $\bar{\gamma}_Y$, $\bar{\delta}_Y$, etc. are identifiable under exogeneity
- But, $\mathbb{E}[\beta_M^{(i)} \times \gamma_Y^{(i)}]$, $\mathbb{E}[\beta_M^{(i)} \times \delta_Y^{(i)}]$, etc. are unidentifiable
- This is essentially a problem of unobserved pre-treatment confounding

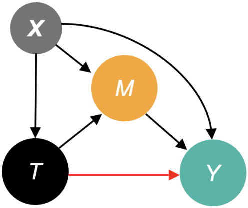
Identification of CDE with Pre-treatment Confounding

- Assumptions:
  1. Unconfoundedness

$$\{Y_i(t,m), M_i(t)\}_{t,m} \perp\!\!\!\perp T_i \mid \boldsymbol{X}_i = \boldsymbol{x}$$
$$\{Y_i(t,m)\}_m \perp\!\!\!\perp M_i \mid T_i = t, \boldsymbol{X}_i = \boldsymbol{x}$$

  2. Overlap

$$P(T_i = t \mid \boldsymbol{X}_i = \boldsymbol{x}) > 0$$
$$P(M_i = m \mid T_i = t, \boldsymbol{X}_i = \boldsymbol{x}) > 0$$



- Identification:

$$\overline{\text{CDE}}(m) = \sum_{\boldsymbol{X}} \left(\mathbb{E}[Y \mid T = 1, M = m, \boldsymbol{X}] - \mathbb{E}[Y \mid T = 0, M = m, \boldsymbol{X}]\right) P(\boldsymbol{X})$$

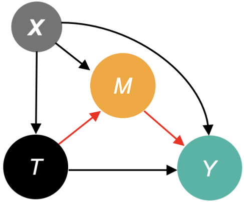
Identification of NDE/NIE with Pretreatment Confounding

- Replace the following assumption

$$\{Y_i(t,m)\}_m \perp\!\!\!\perp \underbrace{M_i}_{=M_i(t)} \mid T_i = t, \mathbf{X}_i = \mathbf{x}$$

with the cross-world independence

$$\{Y_i(t',m)\}_{t',m} \perp\!\!\!\perp M_i(t) \mid T_i = t, \mathbf{X}_i = \mathbf{x}$$



- Additional conditional independence between $Y_i(t',m)$ and $M_i(t)$
- Identification (Imai et al. 2010)

$$\overline{\text{NDE}}(t) = \sum_{M,\mathbf{X}} (\mathbb{E}[Y \mid M, T=1, \mathbf{X}] - \mathbb{E}[Y \mid M, T=0, \mathbf{X}]) \times P(M \mid T=t, \mathbf{X}) P(\mathbf{X})$$

$$\overline{\text{NIE}}(t) = \sum_{M,\mathbf{X}} \mathbb{E}[Y \mid M, T=t, \mathbf{X}] \times \{P(M \mid T=1, \mathbf{X}) - P(M \mid T=0, \mathbf{X})\} P(\mathbf{X})$$

Experimental Identification (Imai et al. 2013)

- Parallel design
  1. Randomize T and observe M and Y
  2. Randomize T and M and observe Y
- We can identify $P(M(t))$, $P(Y(t, M(t))$, and $P(Y(t, m))$
- CDE is identified
- NDE/NIE is still not identifiable:
  - randomization cannot break correlation between $Y(t', m)$ and $M(t)$
  - partial identification: sharp bounds contain zero
- Crossover design
  1. Randomize T and observe M and Y
  2. On the same sample, change T to the opposite condition while holding M at the same value and observe Y
- $Y(t, M(t))$, $M(t)$, and $Y(1 - t, M(t))$ are observable
- Additional assumption: no carryover effects
- NDE/NIE is identifiable

No Interaction Assumption

- No individual-level interaction

$$Y_i(1, m) - Y_i(0, m) = Y_i(1, m') - Y_i(0, m')$$

  - $\text{NDE}_i(t) = \text{CDE}_i(m) = \text{CDE}_i$
  - $\overline{\text{NDE}}(t) = \overline{\text{CDE}}(m) = \overline{\text{CDE}}$
  - $\overline{\text{NIE}}(t) = \text{ATE} - \overline{\text{NDE}}$

- Testable implication:

$$\mathbb{E}[Y_i(1, m) - Y_i(0, m) \mid \boldsymbol{X}_i = \boldsymbol{x}] = \mathbb{E}[Y_i(1, m') - Y_i(0, m') \mid \boldsymbol{X}_i = \boldsymbol{x}]$$

  for all $\boldsymbol{x}$

- NDE/NIE is identifiable so long as CDE can be identified
- Experimental identification, and identification with pretreatment and posttreatment confounding are all possible

Estimation of Natural Direct and Indirect Effects

- Recall the identification formula (NIE)

$$\overline{\text{NIE}}(t) = \sum_{M,\boldsymbol{X}} \mathbb{E}[Y \mid M, T = t, \boldsymbol{X}] \times \{P(M \mid T = 1, \boldsymbol{X}) - P(M \mid T = 0, \boldsymbol{X})\} P(\boldsymbol{X})$$

1. predict M given each treatment value: $\{M_i(1),\ M_i(0)\}$
2. predict Y by first setting $T_i = t$ and $M_i = M_i(0)$, and then $T_i = t$ and $M_i = M_i(1)$: $\{Y_i(t, M_i(0)), Y_i(t, M_i(1))\}$
3. compute the average difference between two predicted outcomes

- Estimation of NDE is similar

$$\overline{\text{NDE}}(t) = \sum_{M,\boldsymbol{X}} (\mathbb{E}[Y \mid M, T = 1, \boldsymbol{X}] - \mathbb{E}[Y \mid M, T = 0, \boldsymbol{X}]) \times P(M \mid T = t, \boldsymbol{X}) P(\boldsymbol{X})$$

- One can also do: $\overline{\text{NDE}}(t) = \text{ATE} - \overline{\text{NIE}}(1 - t)$

Weighting Methods for NDE and NIE

- Three weighting formulae:

$$
\begin{aligned}
\mathbb{E}[Y(t, M(t'))] &= \mathbb{E}\Bigg[\underbrace{\frac{1\{T = t'\}}{\Pr(T = t' \mid \boldsymbol{X})}}_{\text{weighting to get } P(M(t')|\boldsymbol{X})} \times \mathbb{E}[Y \mid M, T = t, \boldsymbol{X}] \Bigg] \\
&= \mathbb{E}\Bigg[\underbrace{\frac{1\{T = t\}}{\Pr(T = t \mid \boldsymbol{X}_i)}}_{\text{treatment weighting}} \times \underbrace{\frac{P(M \mid T = t', \boldsymbol{X})}{P(M \mid T_i = t, \boldsymbol{X}_i)}}_{\text{mediator weighting}} \times Y \Bigg] \\
&= \mathbb{E}\left[\frac{1\{T = t\}}{\Pr(T = t \mid M, \boldsymbol{X})} \times \frac{\Pr(T = t' \mid M, \boldsymbol{X})}{\Pr(T = t' \mid \boldsymbol{X})} \times Y \right]
\end{aligned}
$$

  - The third expression follows from Bayes rule
  - Useful when the mediator is high-dimensional

- Multiply-robust semiparametric estimator (Tchetgen Tchetgen and Shpitser, 2012); Double machine learning (Farbmacher et al. 2022)

Sensitivity Analysis

- Examine the robustness of empirical findings to the violation of untestable assumptions
- How large a departure from the key identification assumption must occur for the conclusions to no longer hold?
- Potential existence of unobserved pretreatment confounding (T is assumed to be unconfounded)

$$\{Y_i(t', m)\}_{t',m} \not\perp\!\!\!\perp M_i(t) \mid T_i = t, \boldsymbol{X}_i = \boldsymbol{x}$$

- Recall LSEM (or more generally, additive semiparametric model)

$$Y_i = \alpha_Y + \beta_Y T_i + \gamma_Y M_i + \underbrace{\lambda_\epsilon U_i + \tilde{\epsilon}_i}_{=\epsilon_i}$$

$$M_i = \alpha_M + \beta_M T_i + \underbrace{\lambda_\eta U_i + \tilde{\eta}_i}_{=\eta_i}$$

- How much does U_i have to matter for the results to go away?

Sensitivity Parameters

- R^2 parameterization
  1. Proportion of previously unexplained variance explained by U_i

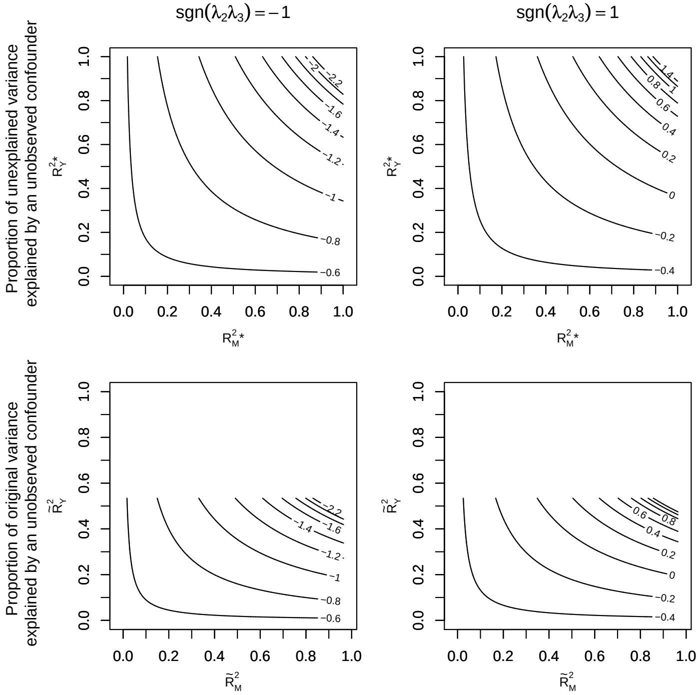
$$R_M^{2*} \equiv \frac{\mathbb{V}(\lambda_\eta U_i)}{\mathbb{V}(\eta_i)} \quad \text{and} \quad R_Y^{2*} \equiv \frac{\mathbb{V}(\lambda_\epsilon U_i)}{\mathbb{V}(\epsilon_i)}$$

  2. Proportion of original variance explained by U_i

$$\widetilde{R}_M^2 \equiv \frac{\mathbb{V}(\lambda_\eta U_i)}{\mathbb{V}(M_i)} \quad \text{and} \quad \widetilde{R}_Y^2 \equiv \frac{\mathbb{V}(\lambda_\epsilon U_i)}{\mathbb{V}(Y_i)}$$

- We also need to specify the direction of effects:

$$\text{sgn}(\lambda_\eta \lambda_\epsilon) = \begin{cases} 1 & \text{if same direction} \\ -1 & \text{if opposite directions} \end{cases}$$


sgn(λ2λ3) = −1
sgn(λ2λ3) = 1
Proportion of unexplained variance explained by an unobserved confounder
Proportion of original variance explained by an unobserved confounder
R_Y^2*
R_M^2*
$\tilde{R}_Y^2$
$\tilde{R}_M^2$
−0.6
−0.8
−1
−1.2
−1.4
−1.6
−2
−2.2
−0.4
−0.2
0
0.2
0.4
0.6
0.8
1
1.4

Gender Bias Application: Standard Mediation Analysis

- The original analysis fits LSEM with interaction

$$Y_i = \alpha_Y + \beta_Y T_i + \gamma_Y M_i + \delta_Y T_i M_i + \boldsymbol{\xi}_Y^\top \boldsymbol{X}_i + \epsilon_i$$
$$M_i = \alpha_M + \beta_M T_i + \boldsymbol{\xi}_M^\top \boldsymbol{X}_i + \eta_i$$

  - Y_i: university admission
  - T_i: the second child is male
  - M_i: sibling size is greater than two

- Estimates:

$\widehat{\text{ATE}}$	0.0020 (0.0013)
$\widehat{\overline{\text{CDE}}(\overline{M})}$	−0.0010 (0.0014)
$\widehat{\overline{\text{NDE}}(1)}$	−0.0001 (0.0014)
$\widehat{\overline{\text{NIE}}(0)}$	0.0022 (0.0005)

- Also, fits a random coefficient model to address heterogeneity
- Sensitivity analysis based on a semiparametric random coefficient model (Imai and Yamamoto, 2013)

Take-aways II

- Linear structural equation model
  - two key assumptions beyond exogeneity:
    1. homogeneous effects
    2. no interaction
  - CDE $=$ NDE under those assumptions
  - Relaxing these assumptions lead to different interpretations and identification issues

- Nonparametric identification analysis under pretreatment confounding
  - CDE is identifiable under standard exogeneity
  - NDE/NIE requires cross-world independence
  - alternatively, CDE $=$ NDE if we assume no individual-level interaction

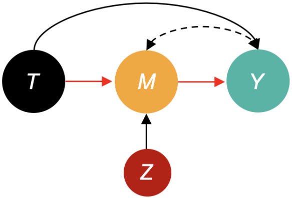
- Difficulty of identification
  - even when M is randomized, NIE/NDE are unidentifiable
  - sensitivity analysis plays an important role for assessing robustness

Part III. Coping with Identification Difficulties

Instrumenting the Mediator

- Instrument: Z_i
- Mediator: $M_i(t, z)$
- Exclusion restriction

$$Y_i(t, m, z) = Y_i(t, m)$$



- NPSEM:

$$\begin{aligned} Y &= f_Y(M, T, \epsilon) \\ M &= f_M(T, Z, \eta) \end{aligned} \quad \text{where} \quad \epsilon \not\perp\!\!\!\perp \eta$$

- If M and Z are continuous, we can use the control function approach (Imbens and Newey, 2009)
  1. Independence: $Z \perp\!\!\!\perp (\epsilon, \eta)$
  2. Monotonicity: η is a continuous scalar variable with its CDF and $f_M(\cdot, \cdot, \eta)$ being strictly monotonic in η
- Then, $(M, T) \perp\!\!\!\perp \epsilon \mid C$ where $C = F_{M \mid T, Z}(T, Z) = F_\eta(\eta)$
  - Recall the control function approach to 2SLS
  - Regress Y on M, T and the first stage residual $\hat{\eta}$
- Extension: an additional instrument for T (Florich and Huber, 2017)

Gender Bias Application: IV Analysis

- Instrument Z: twinning at the second birth

$$M_i = \alpha_M + \beta_M T_i + \zeta_M Z_i + \lambda_M T_i Z_i + \boldsymbol{\xi}_M^\top \boldsymbol{X}_i + \eta_i$$

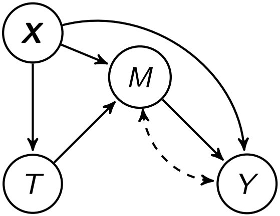
- Assumptions:
  - exogenous instrument: twinning is random conditional on $\boldsymbol{X}$
  - exclusion restriction: twinning affects Y only through M

- Findings:

	Standard analysis	**IV analysis**
$\widehat{\text{ATE}}$	0.0020 (0.0013)	0.0021 (0.0013)
$\widehat{\overline{\text{CDE}}(\overline{M})}$	−0.0010 (0.0014)	−0.0092 (0.0061)
$\widehat{\overline{\text{NDE}}(1)}$	−0.0001 (0.0014)	−0.0203 (0.0106)
$\overline{\text{NIE}}(0)$	0.0022 (0.0005)	0.0224 (0.0105)

Complete Mediation Analysis (Kwon and Roth 2024)

- Complete mediation: $Y_i(t, m) = Y_i(m)$
- Assumption: No unobserved confounding between T and M and between T and Y
- Possible unobserved confounding between M and Y



- Under monotonicity $M_i(1) \geq M_i(0)$ (in the binary mediator case), we can use the following test of instrumental validity

$$P(Y, M = 0 \mid T = 0, \boldsymbol{X}) \geq P(Y, M = 0 \mid T = 1, \boldsymbol{X})$$
$$P(Y, M = 1 \mid T = 1, \boldsymbol{X}) \geq P(Y, M = 1 \mid T = 0, \boldsymbol{X})$$

- Randomized experiment: test of complete mediation
- Observational study: unobserved confounding between T and Y can also lead to the rejection of the null hypothesis

Implicit Mediation

- What if we want to avoid the untestable assumptions at all costs?
- What can we infer from ATE_M and ATE_Y that are identifiable without such assumptions?

Table 1. Possible Implicit-Mediation Findings

Result	Inference	Rationale
X affects M and Y	M may be a mediator.	X appears to influence M, and this effect seems to coincide with a change in Y, as would be expected if M were a mediator.
X affects M but not Y	M appears not to be a mediator.	Although X affects M, this effect seems not to have any consequences for Y.
X affects Y but not M	Some variable other than M may be a mediator.	X appears to have no effect on M, which means that X's apparent effect on Y is not due to changes in M.
X affects neither M nor Y	There seem to be no indirect pathways from X to Y through M or other mediators.	X seems not to set in motion any causal effects.

Bullock and Green (2021)

Identification Analysis of Implicit Mediation

- Questions:
  1. Does $\text{ATE}_M = 0$ imply $\overline{\text{NIE}} = 0$ and/or $\overline{\text{NDE}} \neq 0$?
  2. Does $\text{ATE}_M > 0$ and $\text{ATE}_Y > 0$ imply $\overline{\text{NIE}} > 0$?
- No! Recall even the no-assumption bounds from the parallel experiment design always contain zero
- The decomposition under a binary mediator:

$$\overline{\text{NIE}}(t) = \underbrace{\mathbb{E}[Y_i(t,1) - Y_i(t,0) \mid M(1) = 1, M(0) = 0]}_{\text{ATE of } M \text{ on } Y \text{ for compliers}} \cdot p_{10} - \underbrace{\mathbb{E}[Y_i(t,1) - Y_i(t,0) \mid M(1) = 0, M(0) = 1]}_{\text{ATE of } M \text{ on } Y \text{ for defiers}} \cdot p_{01}$$

  where $p_{m_1 m_0} = \Pr(M(1) = m_1, M(0) = m_0)$
- Cross-world assumption or homogeneity assumption leads to the usual product estimator

$$\overline{\text{NIE}}(t) = \underbrace{\mathbb{E}[Y_i(t,1) - Y_i(t,0)]}_{=\text{ATE of } M \text{ on } Y} \times \underbrace{(p_{10} - p_{01})}_{=\text{ATE}_M}$$

Identification under Monotonicity

(Blackwell et al. 2024; Kwon and Roth 2024)

- Monotonicity assumption (no defier) yields:

$$\overline{\text{NIE}}(t) = \mathbb{E}[Y_i(t,1) - Y_i(t,0) \mid M(1) = 1, M(0) = 0] \cdot p_{10}$$

- Sharp bounds

$$\max\{-\text{ATE}_M, -q_{1-t,t|t}\} \leq \overline{\text{NIE}}(t) \leq \min\{\text{ATE}_M, q_{tt|t}\}$$

where $q_{ym|t} = \Pr(Y = y, M = m \mid T = t)$

- Two fundamental difficulties remain:
  1. effect heterogeneity
  2. endogeneity of mediator
- Even under an additional assumption of $\mathbb{E}[Y(t,1) - Y(t,0)] > 0$, the sharp bounds still contain zero

Take-aways III

- Instrumental variable approach
  - addressing the endogeneity problem
  - the instrument must be exogeneous
  - exclusion restriction needs to be satisfied
  - nonparametric estimation is possible

- Complete mediation
  - hypothesis testing approach
  - no need to assume the exogeneity of mediator
  - no unobserved confounding between T and Y (satisfied in RCT)

- Implicit mediation
  - an attempt to sidestep assumptions
  - not informative even about the signs of NIE/NDE
  - monotonicity is not sufficient

Part IV. Mediation Analysis under Posttreatment Confounding

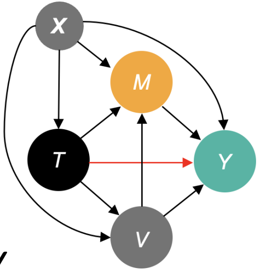
Identification of CDE with Posttreatment Confounding

- Replace the following assumption

$$\{Y_i(t,m)\}_m \perp\!\!\!\perp M_i \mid T_i = t, \boldsymbol{X}_i = \boldsymbol{x},$$

with

$$\{Y_i(t,m)\}_m \perp\!\!\!\perp M_i \mid \boldsymbol{V}_i = \boldsymbol{v}, T_i = t, \boldsymbol{X}_i = \boldsymbol{x}$$



- Post-treatment bias: cannot simply control for $\boldsymbol{V}$

$$\overline{\text{CDE}}(m) \neq \sum_{\boldsymbol{X},\boldsymbol{V}} (\mathbb{E}[Y \mid T=1, M=m, \boldsymbol{X}, \boldsymbol{V}] - \mathbb{E}[Y \mid T=0, M=m, \boldsymbol{X}, \boldsymbol{V}])P(\boldsymbol{X}, \boldsymbol{V})$$

- Identification: model $\boldsymbol{V}$ given T and $\boldsymbol{X}$

$$\overline{\text{CDE}}(m) = \sum_{\boldsymbol{X},\boldsymbol{V}} \{\mathbb{E}[Y \mid T=1, M=m, \boldsymbol{X}, \boldsymbol{V}]P(\boldsymbol{V} \mid T=1, \boldsymbol{X}) - \mathbb{E}[Y \mid T=0, M=m, \boldsymbol{X}, \boldsymbol{V}]P(\boldsymbol{V} \mid T=0, \boldsymbol{X})\}\, P(\boldsymbol{X})$$

Estimation of Controlled Direct Effects

1. Directly use the identification formula

$$\bar{\xi}(m) = \sum_{\boldsymbol{X},\boldsymbol{V}} \{\mathbb{E}[Y \mid T=1, M=m, \boldsymbol{X}, \boldsymbol{V}] P(\boldsymbol{V} \mid T=1, \boldsymbol{X}) - \mathbb{E}(Y \mid T=0, M=m, \boldsymbol{X}, \boldsymbol{V}) P(\boldsymbol{V} \mid T=0, \boldsymbol{X})\} P(\boldsymbol{X})$$

   - regression of Y on $T, M, \boldsymbol{X}, \boldsymbol{V}$
   - model $\boldsymbol{V}$ given T and $\boldsymbol{X}$ $\rightsquigarrow$ difficult if $\boldsymbol{V}$ is high-dimensional

2. Marginal structural models (Robins et al. 2000)

$$\mathbb{E}[Y(t,m)] = \mathbb{E}\left[\underbrace{\frac{1\{T=t, M=m\}}{\Pr(T=t \mid \boldsymbol{X})}}_{\text{IPW for treatment}} \cdot \underbrace{\frac{1}{\Pr(M=m \mid T=t, \boldsymbol{X}, \boldsymbol{V})}}_{\text{IPW for mediator given treatment}} \times Y\right]$$

   - no need to model $\boldsymbol{V}$
   - covariate balancing methods are also available (Imai and Ratkovic, 2015)

Identification of NDE/NIE with Posttreatment Confounding

- Identification is impossible with *observed* posttreatment confounding
- Consider the following NPSEM

$$\begin{aligned} Y &= f_Y(M, \boldsymbol{V}, T, \epsilon) \\ M &= f_M(\boldsymbol{V}, T, \eta) \\ \boldsymbol{V} &= f_{\boldsymbol{V}}(T, \xi) \end{aligned}$$

- Cross-world independence cannot hold

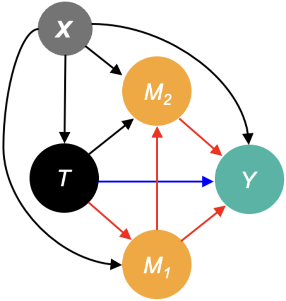
$$\underbrace{\boldsymbol{V}(1)}_{=f_{\boldsymbol{V}}(1,\xi)} \not\perp\!\!\!\perp \underbrace{\boldsymbol{V}(0)}_{=f_{\boldsymbol{V}}(0,\xi)} \quad \Longrightarrow \quad Y(t', m, \boldsymbol{V}(t'), \epsilon) \not\perp\!\!\!\perp M(t, \boldsymbol{V}(t), \eta)$$

- Conditioning on T and $\boldsymbol{V}$ does not solve this problem

Multiple Causally Related Mediators

- Same as the posttreatment confounding setting
- Path specific effects
  1. $T \to Y$
  2. $T \to M_1 \to Y$
  3. $T \to M_2 \to Y$
  4. $T \to M_1 \to M_2 \to Y$
- Combined effect:

$$
\begin{aligned}
& T \to M_1 \rightsquigarrow Y \\
= & (T \to M_1 \to Y) + (T \to M_1 \to M_2 \to Y)
\end{aligned}
$$



- Generalized cross-world independence assumptions:
  1. $\{M_{1i}(t), M_{2i}(t, m_1), Y_i(t, m_1, m_2)\}_{t, \mathbf{m_1}, \mathbf{m_2}} \perp\!\!\!\perp T_i \mid \boldsymbol{X}_i = \boldsymbol{x}$
  2. $\{M_{2i}(t', m_1), Y_i(t', m_1, m_2)\}_{t', \mathbf{m_1}, \mathbf{m_2}} \perp\!\!\!\perp M_{1i}(t) \mid T_i = t, \boldsymbol{X}_i = \boldsymbol{x}$
  3. $\{Y_i(t', m_1, m_2)\}_{t', \mathbf{m_2}} \perp\!\!\!\perp M_{2i}(t, m_1) \mid M_{1i} = m_1, T_i = t, \boldsymbol{X}_i = \boldsymbol{x}$
- Identifiable decomposition:

$$
\text{ATE} = (T \to Y) + (T \to M_2 \to Y) + (T \to M_1 \rightsquigarrow Y)
$$

Interventional Direct and Indirect Effects (IDE and IIE)

- $\mathcal{P}_{M(t)}$: interventional distribution that independently generates $M(t)$
- Definition (Geneletti, 2007; Lok, 2016)

$$\text{Individual: } \begin{cases} \text{IIE}_i(t) & = & Y_i(t, \mathcal{P}_{M(1)}) - Y_i(t, \mathcal{P}_{M(0)}) \\ \text{IDE}_i(t) & = & Y_i(1, \mathcal{P}_{M(t)}) - Y_i(0, \mathcal{P}_{M(t)}) \end{cases}$$

$$\text{Average: } \begin{cases} \overline{\text{IIE}}(t) & = & \mathbb{E}[Y(t, \mathcal{P}_{M(1)}) - Y(t, \mathcal{P}_{M(0)})] \\ \overline{\text{IDE}}(t) & = & \mathbb{E}[Y(t, \mathcal{P}_{M(1)}) - Y(t, \mathcal{P}_{M(0)})] \end{cases}$$

- Interpretation
  - similar to NIE and NDE
  - IDE is a function of CDE:

$$\text{IDE}_i(t) = \sum_m \text{CDE}_i(m) \times P(M(t) = m)$$

  - no mediation: zero treatment effect on M implies zero IIE
- Effect decomposition

$$\underbrace{Y_i(1, \mathcal{P}_{M(1)}) - Y_i(0, \mathcal{P}_{M(0)})}_{\text{Interventional Total Effect (ITE)} \neq \text{TE}} \quad = \quad \text{IIE}_i(t) + \text{IDE}_i(1-t)$$

Identification of IDE and IIE

- Once CDE is identified, we can identify IDE:

$$\overline{\mathsf{IDE}}(t) = \sum_m \overline{\mathsf{CDE}}(m) P(M(t) = m)$$

- IIE is also identifiable:

$$\overline{\mathsf{IIE}}(t) = \sum_m \mathbb{E}[Y(t,m)] \left\{ P(M(1) = m) - P(M(0) = m) \right\}$$

- Effect decomposition

$$\underbrace{\mathbb{E}[Y(1, \mathcal{P}_{M(1)}) - Y(0, \mathcal{P}_{M(0)})]}_{\neq \mathbb{E}[Y(1,M(1)) - Y(0,M(0))]} = \overline{\mathsf{IDE}}(t) + \overline{\mathsf{IIE}}(1-t)$$

- Complete mediation: $\overline{\mathsf{IDE}} = 0$
- Identification is possible with observed pretreatment and posttreatment confounding
- Experimental identification via parallel design is also possible

Take-aways IV

- Posttreatment confounding
  - CDE can be identified under exogeneity
  - estimation of CDE requires marginalizing posttreatment confounders
  - NIE/NDE are not identifiable under exogeneity
  - Different decomposition is identifiable under cross-world independence

- Alternative estimands
  - interventional direct and indirect effects (IDE/IIE)
  - interventional distribution on M
  - enables decomposition of alternative total effect
  - identification of CDE implies that of IDE/IIE

Conclusion, Resources, and References

Concluding Remarks on Causal Mechanisms

- Study of causal mechanisms is essential but challenging
- Triangulation of evidence is necessary
  - causal quantities
    - CDE
    - NDE/NIE, path specific effects
    - IDE/IIE
  - causal identification strategies
    - selection on observables
    - instrumental variables
    - experimental designs
    - partial identification
  - statistical methodologies
    - weighting and regression
    - sensitivity analysis
    - nonparametric modeling and machine learning

Resources

- Statistical software:
  - mediation (R and Stata)
  - Valeri and VanderWeele macros (SPSS, SAS, Stata)

- Review article by an economist:

Huber, Martin (2020). "Mediation Analysis". Handbook of Labor, Human Resources and Population Economics. Ed. by Klaus F. Zimmermann. Cham: Springer.

- Monographs:

VanderWeele, Tyler J. (2015). Explanation in Causal Inference: Methods for Mediation and Interaction. New York: Oxford University Press.

Wodtke, Geoffrey T. and Xiang Zhou (Forthcoming). Causal Mediation Analysis. Cambridge University Press.

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