Identification and Estimation of Marginal Structural Mean Models with Instrumental Variables

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Outline

- Introduction
  - Potential outcome framework
  - Randomization
  - No unmeasured confounders (Rubin et al. 80s)
  - Sequential Randomization Assumption (Robins '80s/'90s)
- Relaxing SRA
  - Instrumental variables
  - Main result
  - Estimation in practice
  - Remarks on assumptions
- Simulation
- Closing remarks

A motivating example

Sports argument: Bill Belichick is a great coach: When average players come to play for him, their performance jumps up; when they leave, they become average again.

Causal framework: Players have a potential outcome, their performance under Belichick and not under Belichick. This pre/post comparison approximates the difference between the potential outcomes.

Sports counter-argument: It's not Belichick. He's just been fortunate . . .

Causal framework: The association between Belichick (treatment) and player performance (outcome) is spurious; it exists due to a confounder. Is there some variable associated with treatment and outcome?

Sports counter-counter-argument: But there was one year when the quarterback was injured, and new players that year also performed better than usual.

Causal framework: There are no unmeasured confounders; we can obtain the causal effect by controlling for the known confounder.

We postulate "potential outcomes," random variables indexed by treatment level

$$Y_a(\omega), a \in \mathcal{A}$$

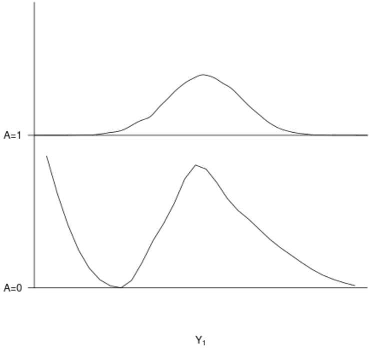
interpreted as the response of a unit ω if, possibly contrary to fact, treatment level a were applied to ω and related to the observed data by the consistency axiom

$$Y = Y_A = Y_a\big|_{a=A}$$

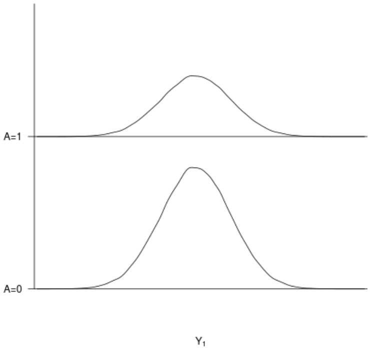
A "causal effect" can then be stated/defined in terms of the potential outcomes, e.g.,

$\mathbb{E}(Y_1 - Y_0)$ "Average Treatment Effect"

Can't say much about Y_1 only knowing $Y_1 \mathbb{1}\{A = 1\}$.



We need to be able to say something about $Y_1 \mathbb{1}\{A = 0\}$ based off of $Y_1 \mathbb{1}\{A = 0\}$



randomization with respect to treatment, $Y_a \perp\!\!\!\perp A$

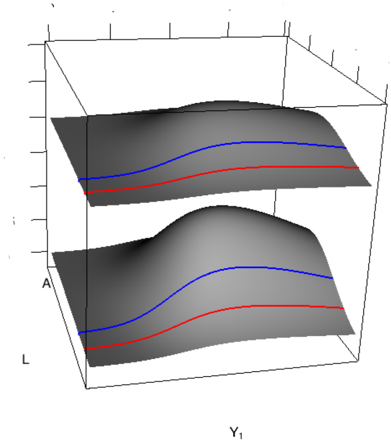
recover Y_1 by dividing $Y\mathbb{1}\{A = 1\}$ by $P(A = 1)$

in general, $\mathbb{E}(g(Y_a)) = \mathbb{E}\left(\frac{g(Y\mathbb{1}\{A=a\})}{f(A)}\right)$

"No Unmeasured Confounders": randomization holds conditional on some covariate L. Compute

$Y_1 \mid L = l$, the potential outcome at each level l, now dividing by the conditional treatment probability ("propensity"). Then integrate over L.

$$\mathbb{E}(g(Y_a)) = \mathbb{E}\left(\frac{\mathbb{1}\{A = a\}g(Y)}{f(A \mid L)}\right)$$

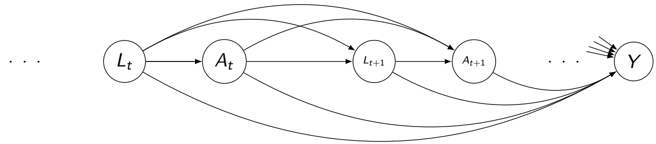


- (clones/copies interpretation) At any covariate level $L = l$, if say, $P(A = 1 \mid L = l) = 1/4$, then there are 3 unobserved units for every observed unit and (no unmeasured confounders) these are homogenous as to Y_1
- (likelihood perspective)

$$\begin{aligned}
&\mathbb{P}(Y = y, A = a, L = l) \\
&\quad = \mathbb{P}(Y = y \mid A = a, L = l)\mathbb{P}(A = a \mid L = l)\mathbb{P}(L = l) \\
&\quad = \mathbb{P}(Y_a = y \mid A = a, L = l)\mathbb{P}(A = a \mid L = l)\mathbb{P}(L = l) \text{ (consistency)} \\
&\quad = \mathbb{P}(Y_a = y \mid L = l)\mathbb{P}(A = a \mid L = l)\mathbb{P}(L = l) \text{ (NUC)}
\end{aligned}$$

$$\begin{aligned}
&\mathbb{P}(Y_a = y, A = a, L = l) \,/\, \mathbb{P}(A = a \mid L = l) \text{ (positivity)} \\
&\quad = \mathbb{P}(Y_a = y, L = l)
\end{aligned}$$

Longitudinal setting: estimating the effect of a treatment regime in the presence of time-varying confounding.
Central example: Estimating time to progression to AIDS under HAART: Physician bases treatment on the patient's CD4 count, that treatment affects CD4 count, which in turn informs a subsequent treatment decision. And CD4 count is prognostic of the outcome.



- T time points $t = 1, \ldots, T$
- Treatment regime $\overline{A} = (A_1, \ldots, A_T) \in \mathcal{A}^T$ discrete-valued
- Potential outcomes $\{Y_{\overline{a}}\}$ indexed by fixed treatment regimes $\overline{a} \in \mathcal{A}^T$
- Observed outcome $Y = Y_{\overline{A}} = \sum_{\overline{a}} \mathbb{1}\{\overline{A} = \overline{a}\} Y_{\overline{a}}$ (consistency)
- Covariates $\overline{L} = (L_1, \ldots, L_T)$

similar targets such as

$$\beta = \mathbb{E}(Y_{\bar{a}}) - \mathbb{E}(Y_{\bar{0}})$$

or

$$\beta_1 : \mathbb{E}(Y_{\bar{a}}) = \beta_0 + \beta_1 \sum_t a_t$$

("marginal structural mean models")

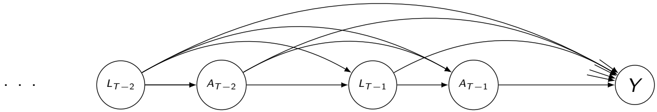
Consider using a regression model to estimate β, e.g.:

$$\mathbb{E}(Y \mid \overline{A} = \overline{a}) = \mathbb{E}(Y_{\overline{a}} \mid \overline{A} = \overline{a}) = b_0 + b_1 \sum_t a_t$$

L_{T-1} is a confounder of the subsequent treatment and the outcome, and so should be accounted for, e.g.,

$$\mathbb{E}(Y \mid \overline{A}, L_{T-1}) = b_0 + \gamma_1 L_{T-1} + b_1 \sum_t A_t$$

on the other hand, controlling for L can block the effect of earlier treatment.



The longitudinal generalization of "no unmeasured confounders" is

- "Sequential randomization assumption": for all $\overline{a}$ and t,

$$Y_{\overline{a}} \perp\!\!\!\perp A_t \mid A_1, \ldots, A_{t-1}, L_1, \ldots, L_t$$

Propensity score weights generalize to

$$W_{SRA} = \Pi_{t=1}^{T} f_{A_t|\overline{A}_{t-1},\overline{L}_t}(A_t \mid \overline{A}_{t-1}, \overline{L}_t)$$

SRA will hold when all factors prognostic of Y used by the physicians to determine whether treatment A is given at t are recorded in $\overline{A}_{t-1}, \overline{L}_t$

A marginal structural mean model ("MSMM") is a model on the marginal mean of the potential outcomes,

$$\mathbb{E}(Y_{\overline{a}}) = \mu_\beta(\overline{a})$$

Besides SRA, also assume $0 < \mathbb{P}(A_t = a \mid \overline{L}_{t-1}, \overline{A}_{t-1}) < 1$ when the conditioning event has positive probability

Then (Robins '98)

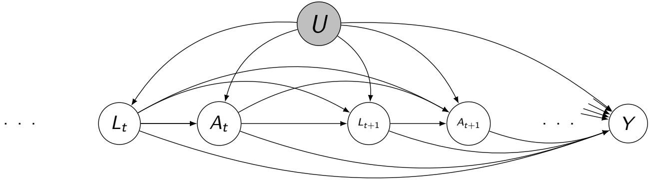
$$\mathbb{E}((Y - \mu_\beta(\overline{A}))/W_{SRA}) = 0.$$

- $\hat{\beta}$ asymptotically normal (usual regularity conditions)
- Standard software routines can be used, as long as they allow observations to be weighted
- similar change of measure interpretation as NUC theory

Outline

Suppose there is some unobserved confounder U, which we would need to have observed in order for "SRA" to hold:

$$Y_{\bar{a}} \perp\!\!\!\perp A_t \mid \overline{A}_{t-1}, \overline{L}_{t-1}, \overline{U}_{t-1} \quad \text{for all } t, \bar{a}$$



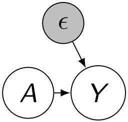
Can we still identify/estimate the causal parameter?

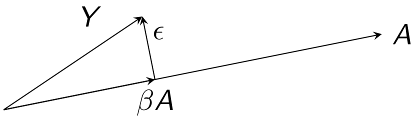
Informally, an IV is a random variable associated with covariates, but orthogonal to the unobserved confounder.

A typical application is OLS with "endogenous error"

$$Y = \beta A + \epsilon$$

Consistency of OLS generally requires ϵ be uncorrelated with A





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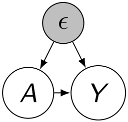
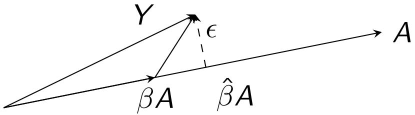
If in fact the error is correlated with the covariates, OLS is biased





Informally, an IV is a random variable associated with covariates, but orthogonal to the unobserved confounder.

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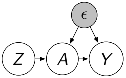
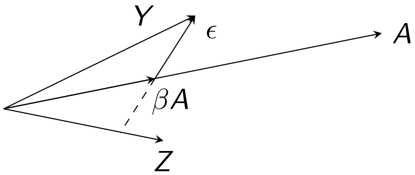
$$Y = \beta A + \epsilon$$

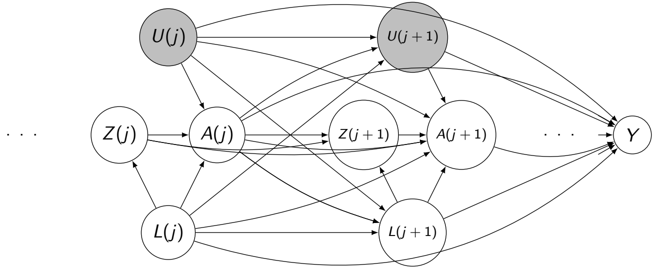
Suppose we have a random variable Z orthogonal to ϵ, but not to A.





Examples of instrumental variables:

- assignment to treatment
- physician preference
- draft status
- distance to school/hospital



Assumptions

1. $Y_{\overline{a}} \perp\!\!\!\perp A_t \mid \overline{A}_{t-1}, \overline{L}_{t-1}, \overline{U}_{t-1}$ for all $t, \overline{a}$
2. IV assumptions
   - 2.1 $Y_{\overline{az}} = Y_{\overline{a}}$ a.s. "exclusion restriction"
   - 2.2 $Z_t \perp\!\!\!\perp \overline{U} \mid \overline{A}_{t-1}, \overline{Z}_{t-1}, \overline{L}_t$ "IV independence A"
   - 2.3 $\overline{Z} \perp\!\!\!\perp Y_{\overline{a}} \mid \overline{A}, \overline{L}$ "IV independence B"
3. and finally an assumption specific to our problem . . .

3. An assumption specific to our problem, either of:

    3.1 Independent Compliance Type:

$$\mathbb{E}\left[A_t | \overline{U}_t, \overline{L}_t, \overline{A}_{t-1}, \overline{Z}_{t-1}, Z_t = 1\right] - \mathbb{E}\left[A_t | \overline{U}_t, \overline{L}_t, \overline{A}_{t-1}, \overline{Z}_{t-1}, Z_t = 0\right]$$
$$= \Delta_t\left(\overline{L}_t, \overline{A}_{t-1}, \overline{Z}_{t-1}\right)$$

    or

    3.2 Independent Causal Effect (binary treatment only):

$$Y_{(a_t=1, a_{t+1}, \ldots, a_T)} - Y_{(a_t=0, a_{t+1}, \ldots, a_T)} \perp\!\!\!\perp \overline{U}_t \mid \overline{L}_t, \overline{A}_{t-1}, \overline{Z}_{t-1}$$

Weighted Estimating Equation
Define weights by

$$\overline{W} = \prod_{t=1}^{T} (-1)^{1-Z_t} \Delta_t \left(\overline{L}_t, \overline{A}_{t-1}, \overline{Z}_{t-1} \right) f_{Z_t}(Z_t \mid \overline{A}_{t-1}, \overline{Z}_{t-1} \overline{L}_t).$$

Let h denote a vector-valued function of $\overline{A}$ of the same dimension as β. Under the above assumptions,

$$\mathbb{E}\left(h(\overline{A})(Y - \mu_\beta(\overline{A}))/\overline{W} \right) = \sum_{\overline{a}} h(\overline{a}) \left(\mathbb{E}(Y_{\overline{a}}) - \mu_\beta(\overline{a}) \right) (-1)^{T - \sum_j a_j} = 0$$

where the summation is taken over all tuples $\overline{a} \in \{0, 1\}^{T-1}$

$f_{Z_t|\overline{A}_{t-1},\overline{Z}_{t-1},\overline{L}_t}$ and $\Delta_t(\overline{A}_{t-1},\overline{Z}_{t-1},\overline{L}_t)$ require modeling/estimation

bootstrap or sandwich variance for inference

weight stabilization analogous to SRA theory

3.1 “independent compliance type”

Interpretation: Z_j assignment to treatment or control A_j the treatment actually received assumption is that the difference in proportions of compliance is accounted for by the observed data

.

		$A_{Z=0}$	
		0	1
$A_{Z=1}$	0	never-taker	defier
	1	complier	always-taker

3.2 "independent causal effect"

assume A is binary. The assumption implies you could obtain the ATE at a time point, i.e., β_1 in the model $E(Y_{(\bar{a}_{j-1},a_j)}) = \beta_0 + \beta_1 a_j$, using non-IV methods. The theorem allows you to go from here to estimating the causal parameter in an arbitrary mean model.

Special case

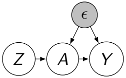
- $T = 1$ time point
- A, Z binary
- $\Delta_j\left(\overline{L}_j, \overline{A}_{j-1}, \overline{Z}_{j-1}\right) = \Delta_j(\overline{A}_{j-1})$
- $f_{Z_j|\overline{A}_{j-1},\overline{Z}_{j-1},\overline{L}_j}$ constant

Consider the saturated model

$$\mathbb{E}(Y_a) = \beta_0 + \beta_1 a = \mathbb{E}(Y_0) + (\mathbb{E}(Y_1) - \mathbb{E}(Y_0))a$$

The weights are now $(-1)^{1-Z}$, and

$$\hat{\beta}_1 = \frac{\sum y_t \mathbb{1}\{z_t = 1\} - \sum y_t \mathbb{1}\{z_t = 0\}}{\sum a_t \mathbb{1}\{z_t = 1\} - \sum a_t \mathbb{1}\{z_t = 0\}}$$



A perspective on the proposed assumptions:

We have an analogue of Robins's g-formula:

$$\mu_\beta(\overline{a}) = \mathbb{E}(Y_{\overline{a}}) =$$
$$\int \mathbb{E}(Y \mid \overline{A} = \overline{a}, \overline{L}, \overline{U}) \prod_j f_{L_j, U_j \mid \overline{A}_{j-1}, \overline{L}_{j-1}, \overline{U}_{j-1}}(l_j, u_j \mid \overline{a}_{j-1}, \overline{l}_{j-1}, \overline{u}_{j-1}) d\nu(l_j, u_j)$$

$$0 = \int \left(\mathbb{E}(Y \mid \overline{A}, \overline{L}, \overline{U}) - \mu_\beta(\overline{A})\right) \prod_j f_{L_j, U_j \mid \overline{A}_{j-1}, \overline{L}_{j-1}, \overline{U}_{j-1}}(l_j, u_j \mid \overline{a}_{j-1}, \overline{l}_{j-1}, \overline{u}_{j-1}) d\nu(l_j, u_j)$$

Decompose the error as

$$Y - \mu_\beta(\overline{A}) = \underbrace{Y - E(Y \mid \overline{A}, \overline{Z}, \overline{L}, \overline{U})}_{\text{exogenous}} + \underbrace{E(Y \mid \overline{A}, \overline{Z}, \overline{L}, \overline{U}) - \mu_\beta(\overline{A})}_{\text{``}\eta\text{'', endogenous}}$$

Using the "g-formula" analogue,

$$\begin{aligned}\eta &= \sum_{\overline{a}} \mathbb{1}\{\overline{A} = \overline{a}\} \sum_{t=1}^{T} \phi_t^{(\overline{a})}(\overline{A}_{t-1}, \overline{L}_t) - \mathbb{E}\left(\phi_t^{(\overline{a})}(\overline{A}_{t-1}, \overline{L}_t) \mid \overline{A}_{t-1}, \overline{L}_{t-1}\right) \\ &= \sum_{\overline{a}} \mathbb{1}\{\overline{A} = \overline{a}\} M^{(\overline{a})}\end{aligned}$$

for some $\phi_t^{(\overline{a})}$, a sum of martingales at each level of A

We seek functions of the observed data $w(\overline{A}, \overline{L}, \overline{Z})$ to form estimating equations

$$\mathbb{E}(w(\overline{A}, \overline{L}, \overline{Z}) \times (Y - \mu_\beta(\overline{A}))) = \mathbb{E}(w(\overline{A}, \overline{L}, \overline{Z}) \times \eta) = 0$$

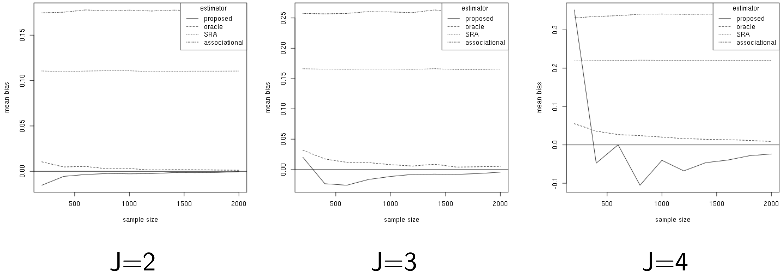
We could treat this as an IV problem (η and A are dependent), simply requiring a random variable Z orthogonal to η

But we know more about the structure of η.

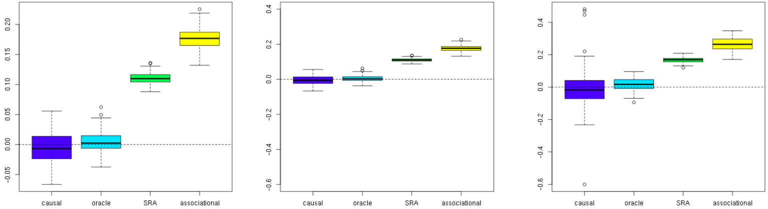
Under the proposed conditions the quantities $1/\overline{W}$ are orthogonal to η

Outline

"Independent compliance type" assumption holds, "independent causal effect" does not hold



Mean bias versus sample size of the weighted estimator, for J=2, 3, and 4, time points, compared with oracle (weights including observed and unobserved confounders), SRA (weights including observed confounders), and associational (no weighting) estimators.



J=2 J=2 (axis rescaled) J=3

N=500

Outline

target application: SMART trials

see Wharton tech report (Tchetgen Tchetgen, Michael, Cui '18) for

- identification of the parameters of any marginal structural models, e.g., failure time model or quantile model
- semiparametric efficient, multiply robust estimator partially protects against model misspecification in that the estimator is consistent whenever any one of three sets of nuisance parameters are consistently estimated

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