A Semiparametric Instrumental Variable Approach to Optimal Treatment Regimes Under Endogeneity

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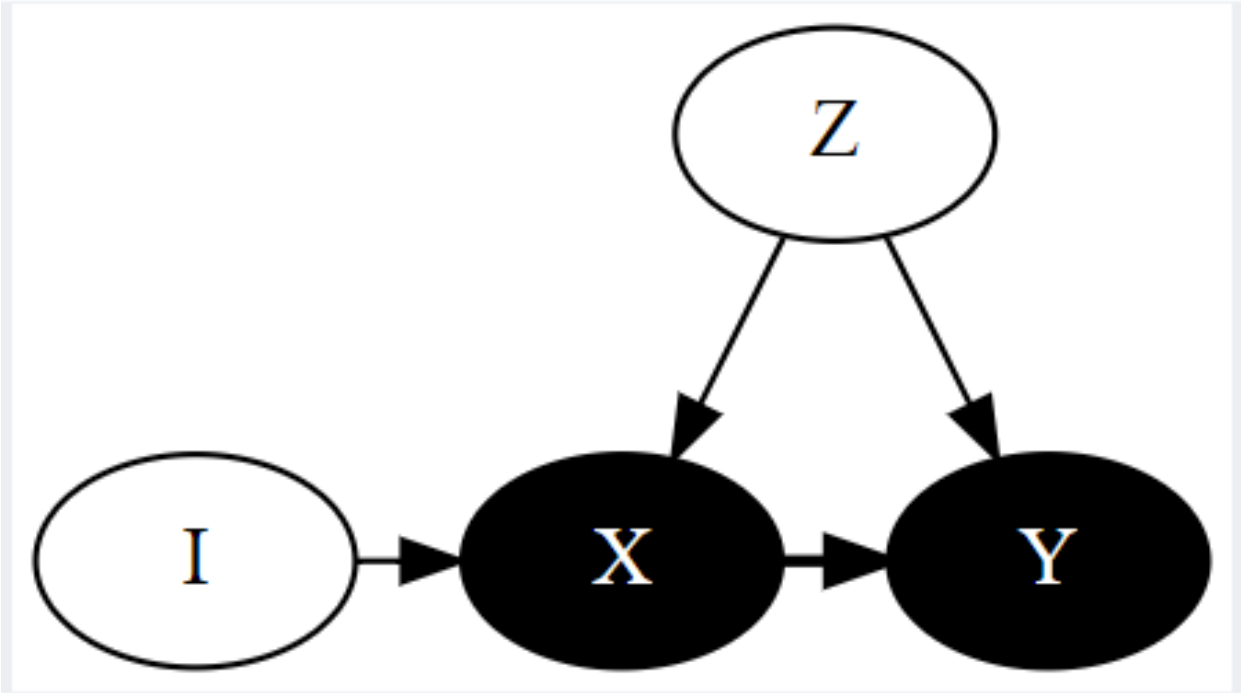
Introduction

- Primary goal of an individualized treatment regime is to cover a rule to assign treatment
- An alternative classification approach has emerged to estimate optimal treatment regime (OTR) [Rubin and van der Laan 2012; Zhang, Tsiatis, Davidian, et al. 2012; Zhao et al. 2012]
- NUC is not guaranteed in observational studies, nor in randomized experiments subject to non-compliance
- The central controversy to comply unconfoundedness is to account for a large number of relevant covariates
- Without NUC, OTR cannot be identified
- In such a situation, instrumental variable (IV) approach is well-known to estimate causal effects in observational or randomized trials with non-compliance

Introduction

- **Instrumental Variable:** An IV is defined as a pretreatment variable that is independent of all unmeasured confounders and does not have a direct causal effect on the outcome other than through the treatment



Introduction

- This paper propose a general instrumental variable (IV) approach to learning optimal treatment regimes in case NUC fails to hold
- Basically, they adapted and extended the weighted classification perspective pioneered by Zhang, Tsiatis, Davidian, et al. (2012), Zhao et al. (2012), and Rubin and van der Laan (2012), by allowing for an endogenous treatment

Methodology

- Notations:
  - Y denote the outcome of interest
  - $A \in \{-1, 1\}$
  - U is an unmeasured confounder of the effect of A on Y
  - $Z \in \{-1, 1\}$ denote pretreatment IV
  - $L \in \mathcal{L}$ denote a set of fully observed pre-IV covariates
  - Complete data $= (Y, L, A, U, Z)$ and observed data $= (Y, L, A, Z)$
- Objective is to estimate an optimal treatment regime $\mathcal{D} : \mathcal{L} \mapsto \{-1, 1\}$ as follows:

$$\mathcal{D}^*(L) = \text{sign}\{E(Y_1 - Y_{-1}|L)\} \tag{1}$$

where Y_a is a person's potential outcome under an intervention that sets treatment to value a

Methodology

- Let $Y_{\mathcal{D}(L)}$ be the potential outcome under a hypothetical intervention that assigns treatment according to regime $\mathcal{D}$

$$Y_{\mathcal{D}(L)} = Y_1 \; I\{\mathcal{D}(L) = 1\} + Y_{-1} \; I\{\mathcal{D}(L) = -1\} \tag{2}$$

Assumptions

- **Assumption 1 (Unconfoundedness):** $Y_a \perp\!\!\!\perp A|L$
- Under this assumption, OTR are identified from the observed data as follows:

$$\mathcal{D}^*(L) = \text{sign}\{E(Y|L, A = 1) - E(Y|L, A = -1)\} \tag{3}$$

- Qian and Murphy (2011) established an alternative approach to estimate OTR as follows:

$$\begin{aligned}\mathcal{D}^*(L) &= \underset{\mathcal{D}}{\text{argmax}} E_L[E_{Y_{\mathcal{D}}}\{Y_{\mathcal{D}(L)}|L\}] \\ &= \underset{\mathcal{D}}{\text{argmax}} E\left[\frac{I\{A = \mathcal{D}(L)\}Y}{f(A|L)}\right]\end{aligned} \tag{4}$$

- Let $P^{\mathcal{D}}$ denote the distribution of (L, A, Y) in which $\mathcal{D}$ is used to assign treatment A. The likelihoods under $p^{\mathcal{D}}$ and P are:

$$dP^{\mathcal{D}}(L, A, Y) = f_0(L)\, f_1(Y|L, A)\, I\{A = \mathcal{D}(L)\}$$
$$dP(L, A, Y) = f_0(L)\, f_1(Y|L, A)\, f(A|L)$$

- Now,

$$E\{Y_{\mathcal{D}(L)}\} = \int Y\, dP^{\mathcal{D}} = \int Y \frac{dP^{\mathcal{D}}}{dP} dP = E\left[\frac{I\{A = \mathcal{D}(L)\}Y}{f(A|L)}\right] \quad (5)$$

- Zhao et al. (2012) and Zhang, Tsiatis, Davidian, et al. (2012) transformed the maximization problem into a classification problem as follows:

$$\mathcal{D}^*(L) = \underset{\mathcal{D}}{\text{argmax}} E\left[\frac{Y}{f(A|L)} I\{A \neq \mathcal{D}(L)\}\right] \tag{6}$$

  with 0-1 loss function and weight $\frac{Y}{f(A|L)}$
- Minimizing equation (6) is difficult due to discontinuity and non-convexity of 0-1 loss
- Zhao et al. (2012) addressed this issue to find a convex surrogate loss by substituting the 0-1 loss with the hinge loss and proposed to solve the optimization via support vector machines

Assumptions for the identification of OTR with unmeasured confounding

- Let $Y_{z,a}$ denote the potential outcome had a person's IV and treatment value has been set to z and a, respectively
- **Assumption 2 (Latent unconfoundedness):**

$$Y_{z,a} \perp\!\!\!\perp (Z, A) | L, U \text{ for } z, a = \pm 1$$

  together L and U suffices to account for confounding of the joint effect of Z and A on Y
- **Assumption 3 (IV relevance)** $Z \not\perp\!\!\!\perp A | L$
- **Assumption 4 (Exclusion restriction)** $Y_{z,a} = Y_a$ for $z, a = \pm 1$ almost surely
  i.e., there can be no direct causal effect of Z on Y not mediated by A

- **Assumption 5 (IV independence):**

$$Z \perp\!\!\!\perp U | L$$

This assumption states that the causal effect of Z on Y is unconfounded given L

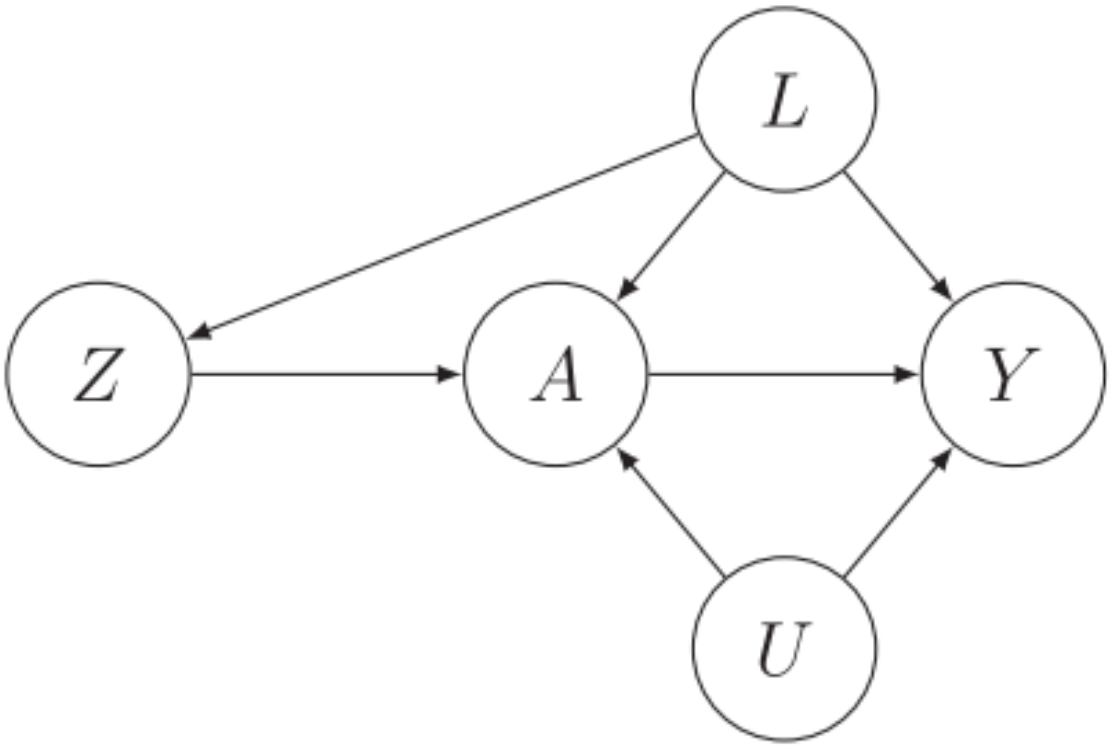


Figure 1. Causal DAG with unmeasured confounding and a causal IV.

- **Assumption 6 (IV positivity):**

$$0 < f(Z = 1|L) < 1$$

- Above assumptions are not enough to identify $\mathcal{D}^*$
- **Assumption 7 (No unmeasured common effect modifier):**

$$Cov\left\{\tilde{\delta}(L, U), \tilde{\gamma}(L, U)\right\} = 0, \text{ almost surely}$$

$$\tilde{\delta}(L, U) = Pr(A = 1|Z = 1, L, U) - Pr(A = 1|Z = -1, L, U)$$
$$\tilde{\gamma}(L, U) = E(Y_1 - Y_{-1}|L, U)$$

- **Assumption 8 (Independent compliance type):**

$$\delta(L) = Pr(A = 1|Z = 1, L) - Pr(A = 1|Z = -1, L) = \tilde{\delta}(L, U)$$

this assumption will hold if U was independent of a person's compliance type

- Theorem 2.1: Under Assumptions 2–7, $E(Y_{\mathcal{D}_L})$ is nonparametrically identified as:

$$\underset{\mathcal{D}}{\text{argmax}} E(Y_{\mathcal{D}_L}) = \underset{\mathcal{D}}{\text{argmax}}\, E\left[\frac{ZAY\, I\{A = \mathcal{D}(L)\}}{\delta(L)f(Z|L)}\right] \tag{7}$$

Furthermore, under Assumptions 2–6 and 8, for a given regime $\mathcal{D}$,

$$E(Y_{\mathcal{D}_L}) = \nu(\mathcal{D}) = E\left[\frac{ZAY\, I\{A = \mathcal{D}(L)\}}{\delta(L)f(Z|L)}\right]$$

- Theorem 2.2: Under Assumptions 2–7,

$$\underset{\mathcal{D}}{\operatorname{argmax}}\, E[Y_{\mathcal{D}(L)}] = \underset{\mathcal{D}}{\operatorname{argmax}}\, E\left[\frac{Y\, I\{Z = \mathcal{D}(L)\}}{\delta(L) f(Z|L)}\right] \tag{8}$$

  This theorem states that if $\delta(L) > 0$ is known a priori, then it is possible to identify OTR without observing A by solving optimization problem $E[\tilde{W}(L)\, I\{Z = \mathcal{D}(L)\} Y / f(Z|L)]$

- Basically, authors used IV to estimate the conditional treatment effect for a subpopulation of patients who are induced to receive treatment by the IV, and then use this estimate to construct the optimal treatment regime

Classification approach

- Motivated from Theorem 2.1 and 2.2, equations 7 and 8 reduces to the optimization problem:

$$\underset{\mathcal{D}}{\text{argmin}} \left[W^{(1)} I\{A \neq \mathcal{D}(L)\} \right] \tag{9}$$

$$\underset{\mathcal{D}}{\text{argmin}} \left[W^{(2)} I\{Z \neq \mathcal{D}(L)\} \right] \tag{10}$$

where

$$W^{(1)} = \frac{ZAY}{\delta(L) f(Z|L)}, \quad W^{(2)} = \frac{Y}{\delta(L) f(Z|L)}$$

- This paper proposed to estimate optimal treatment regimes by minimizing the following regularized objective function,

$$\hat{g} = \underset{g}{\operatorname{argmin}} \frac{1}{n} \sum_{i=1}^{n} |W_i| \, \phi\left(sign(W_i) A_i g(L_i)\right) + \frac{\lambda}{2} ||g||^2 \tag{11}$$

$$\hat{\mathcal{D}} = \operatorname{sign}(\hat{g}) \tag{12}$$

- First, weight W_i is estimated from the data using the formula of $W^{(1)}$, and then will substitute in (11)
- $\hat{\delta}(L)$ and $\hat{f}(Z|L)$ are fitted by logistic regression or random forest
- Decision function $g(L_i)$ can be a linear or non-linear function of L_i

Multiply robust classification-based estimators

- One could estimate optimal treatment regimes over a class of parametric models of regimes
- This kind of approach may restrict treatment regimes to a relatively small set of possible functions and therefore may be suboptimal
- An alternative is to develop a multiply robust classification based estimator
- Denote the conditional ATE as: $\Delta(L) = E(Y_1 - Y_{-1}|L)$
- Minimize $E\left[A\Delta(L)I\{A \neq \mathcal{D}(L)\}\right]$ or $E\left[\Delta(L)I\{Z \neq \mathcal{D}(L)\}/Z\right]$ with respect to $\mathcal{D}$
- This choice of statistic $\tilde{\Delta}(L) = \frac{ZY}{\delta(L)f(Z|L)}$ gives us the usual format discussed earlier

- Motivated by the form of the efficient influence function of $E[\Delta(L)]$(Wang and Tchetgen Tchetgen 2018), this paper proposes:

$$\tilde{\Delta}_{MR}(L) = \frac{Z}{\delta(L)f(Z|L)}\{Y - A\Delta(L) - E[Y|Z=-1,L] + \Delta(L)E[A|Z=-1,L]\} + \Delta(L)$$

to obtain weights

$$\hat{W}^{(1)}_{MR} = \frac{ZA}{\delta(L;\hat{\beta})\hat{f}(Z|L)}\{Y - A\Delta(L;\hat{\theta}) - \hat{E}[Y|Z=-1,L] + \Delta(L;\hat{\theta})\hat{E}[A|Z=-1,L]\} + A\Delta(L,\hat{\theta})$$

$$\hat{W}^{(2)}_{MR} = \frac{1}{\delta(L;\hat{\beta})\hat{f}(Z|L)}\{Y - A\Delta(L;\hat{\theta}) - \hat{E}[Y|Z=-1,L] + \Delta(L;\hat{\theta})\hat{E}[A|Z=-1,L]\} + Z\Delta(L,\hat{\theta})$$

- It is called multiply robust in the sense of maximizing the value function (or minimizing the weighted classification error) in the union of the following models:

$$\mathcal{M}_1' : \text{models for } f(Z|L) \text{ and } \delta(L) \text{ are correct}$$
$$\mathcal{M}_2' : \text{models for } f(Z|L) \text{ and } \Delta(L) \text{ are correct}$$
$$\mathcal{M}_3' : \text{models for } \Delta(L),\ E[Y|Z=-1,L],\ \delta(L),\ \text{and } E[A|Z=-1,L] \text{ are correct}$$

Simulation

- $Pr(A = 1|L, Z, U) = \text{expit}(2L^{(1)} + 2.5Z - 0.5U)$ with Z a Bernoulli event with probability $1/2$, and U from a bridge distribution with parameter $\phi = 1/2$ because U connects the treatment assignment mechanism and the outcome
- By a theorem of Wang and Louis (2003), $\text{logit}\{Pr(A = 1|L, Z)\} = \alpha^T(1, L, Z)$ so that upon marginalizing over U the model for $f(A|L, Z)$ remains a logistic regression
- $\hat{f}(Z|L), \hat{f}(A|L, Z)$ are estimated from logistic regression models
- $\hat{E}(Y|L, Z)$ is estimated from a linear regression model

- Considered four scenarios for the outcome model as:

$$Y = h(L) + q(L)A + \epsilon$$
$$Y = h(L) + q(L)A + 0.5U + \epsilon$$
$$Y = exp\{h(L) + q(L)A\} + \epsilon$$
$$Y = exp\{h(L) + q(L)A\} + U + \epsilon$$

where

$$h(L) = (0.5 + 0.5L^{(1)} + 0.8L^{(2)} + 0.3L^{(3)} - 0.5L^{(4)} + O.7L^{(7)})$$

$$q(L) = (0.2 - 0.6L^{(1)} - 0.8L^{(2)}$$

Kernel	OWL	RWL	IV-IW	IV-MR
Linear	96.0 (2.9)	97.3 (1.8)	95.6 (4.8)	96.9 (2.9)
Non-linear	87.6 (7.5)	95.4 (3.1)	89.3 (9.0)	93.4 (5.7)
Linear	35.9 (17.3)	37.9 (18.4)	91.5 (7.6)	92.3 (7.2)
Non-linear	61.2 (9.9)	61.4 (10.2)	81.8 (11.3)	85.4 (9.7)
Linear	356.5 (4.4)	359.4 (2.5)	358.5 (3.4)	358.9 (3.1)
Non-linear	297.0 (33.0)	356.6 (4.4)	315.8 (34.6)	354.7 (8.4)
Linear	275.1 (4.6)	275.8 (6.6)	349.1 (12.1)	349.8 (10.1)
Non-linear	280.4 (13.2)	298.2 (14.0)	308.3 (33.8)	331.2 (23.0)

Table: Mean and SD of value functions

Conclusion and Future direction

- In this paper, general IV approach is introduced to learning optimal treatment regimes under endogeneity
- Established identification of value functions and OTR through IV approach
- Sometimes the values of instruments are unknown and must be estimated using the data. Understanding the implication for inference of empirically defining IV is a fruitful avenue of future research
- The proposed methods can also be modified in case of a censored survival outcome by accounting for possibly dependent censoring
- Extension of this method for multicategory treatment options, as well as, multicategory classification problem
- Extension of this method for a multiple sequence of decision rules is also a future direction

Thank You!

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