TMLE for Marginal Structural Models Based on Instrument

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Abstract
We consider estimation of a causal effect of a possibly continuous treatment when treatment assignment is potentially subject to unmeasured confounding, but an instrument is available. Our semiparametric structural equation for the outcome as a function of treatment and covariates assumes that the effect of treatment is linear, conditional on the observed baseline covariates. This weakens the commonly made linearity assumption. The structural equation also assumes that the conditional mean of its error, given the instrument and baseline covariates, equals zero, which is the typical instrumental variable assumption. We establish identifiability of marginal causal effects of the treatment as defined by projections of the true causal dose-response curve onto a user supplied working marginal structural model. We derive the efficient influence curve of the resulting statistical parameter/estimand, and develop a targeted minimum loss-based estimator of this estimand. The TMLE can be viewed as a generalization of the two-stage regression method in the instrumental variable methodology to semiparametric models. The asymptotic efficiency and robustness of this substitution estimator is outlined. Finally, we implement this new estimator and evaluate its performance through a simulation study.

Keywords: Asymptotic linearity of an estimator, causal effect, efficient influence curve, empirical process, confounding, influence curve, instrument, loss function, semiparametric statistical model, targeted maximum likelihood estimation, targeted minimum loss based estimation (TMLE).

1. Introduction

2. Formulation of statistical estimation problem

We observe n i.i.d. copies $O_1, \ldots, O_n$ of a random variable $O = (W, R, A, Y) \sim P_0$, where P_0 is its probability distribution. Here W denotes the measured baseline-covariates, R denotes the subsequent (in time) realized instrument that is believed to only affect the final outcome Y through the intermediate treatment variable A. The goal of the study is to assess a causal effect of treatment A on outcome Y. We consider the case in which it would be inappropriate to assume that W denotes all confounders: i.e., it is believed that A is a function of both the measured W, but also unmeasured confounders. As a consequence, methods that rely on the no unmeasured confounding assumption would most likely be biased. In order to deal with the unmeasured confounding, the instrumental variable assumption is absolutely crucial. To formally define the causal quantity of interest and

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establish its identifiability from the observed data distribution P_0, we assume the following structural equation model: $W = f_W(U_W)$, $R = f_R(W, U_R)$, $A = f_A(W, R, U_A)$, $Y = Am_0(W) + \theta_0(W) + U_Y$, where $U = (U_W, U_R, U_A, U_Y) \sim P_{U,0}$ is an exogenous random variable, f_W, f_R, f_A, m_0, and θ_0 are all unspecified. In addition, it is assumed that $E(U_Y \mid R, W) = 0$, which holds in particular if U_R is independent of U_Y, given W. In other words, even though we did not assume that A is randomized conditionally on W, we are assuming that R is randomized conditionally on W. In addition, we made an important exclusion restriction assumption by not including R in the equation for Y: thus, it is assumed that R does not have a direct effect on Y. In a later section, we will also consider the more restrictive model that assumes that m_0 satisfies a particular parametric form $m_0(W) = m_{\alpha_0}(W)$ for some model $\{m_\alpha : \alpha \in \mathbb{R}^k\}$.

This structural equation model allows one to define counterfactuals $Y(a) = am_0(W) + \theta_0(W) + U_Y$ for all possible values $a \in \mathcal{A}$, where $\mathcal{A}$ denotes a support of A. We can now define marginal causal effects $E_0(Y(a) - Y(0)) = aEm_0(W)$ or adjusted causal effects $E_0(Y(a) - Y(0) \mid V) = aE(m_0(W) \mid V)$ conditional on a user supplied covariate $V \subset W$. These causal effects are functions of m_0 and the distribution of W. **Identification of m_0:** Let $\Pi_0(R, W) \equiv E_0(A \mid R, W)$ be the conditional mean of A, given R, W. The instrumental variable assumption $E(U_Y \mid R, W) = 0$ implies

$$E_0(Y \mid \Pi_0(R, W), W) = \Pi_0(R, W)m_0(W) + \theta_0(W).$$

This demonstrates that our structural equation model implies a semiparametric regression model for the conditional mean of Y, given $W, \Pi_0(R, W)$. As a consequence, we can identify the regression $\bar{Q}_0(R, W) = E_0(Y \mid \Pi_0(R, W), W)$, or, equivalently, (m_0, θ_0) that identifies this regression, by minimizing the risk of the squared error loss $L_{\pi_0}(m, \theta)(O) = (Y - \Pi_0(R, W)m(W) - \theta(W))^2$:

$$(m_0, \theta_0) = \arg\min_{m,\theta} E_0(Y - \Pi_0(R, W)m(W) - \theta(W))^2.$$

For a pair of values r and r_1, we have

$$E_0(Y \mid R = r, W) - E_0(Y \mid R = r_1, W) = \{\Pi_0(r, W) - \Pi_0(r_1, W)\}m_0(W).$$

Thus, for each w in the support of W, if there exist at least two values $r = r(w)$ and $r_1 = r_1(w)$ in the support of the conditional distribution $g_{R,0}$ of R, given $W = w$, for which $\Pi_0(r, w) - \Pi_0(r_1, w) \neq 0$, then $m_0(w)$ is identified by

$$m_0(w) = \frac{E_0(Y \mid R = r, W = w) - E_0(Y \mid R = r_1, W = w)}{\Pi_0(r, w) - \Pi_0(r_1, w)}.$$

We state this identifiability result for m_0 as a formal lemma.

Lemma 1 *Let $\Pi_0(R, W) \equiv E_0(A \mid R, W)$. Let $g_{R,0}$ be the conditional probability distribution of R, given W. Let $\mathcal{W}$ be a support of the distribution $P_{W,0}$ of W. Let*

$w \in \mathcal{W}$. If there exists two values (r, r_1) in a support of $g_{R,0}(\cdot \mid W = w)$ for which $\Pi_0(r, w) - \Pi_0(r_1, w) \neq 0$, then

$$m_0(w) = \frac{E_0(Y \mid R = r, W = w) - E_0(Y \mid R = r_1, W = w)}{\Pi_0(r, w) - \Pi_0(r_1, w)},$$

which demonstrates that $m_0(w)$ is identified as a function of P_0.

Statistical model: The above stated causal model implies the statistical model $\mathcal{M}$ consisting of all probability distributions P of $O = (W, R, A, Y)$ satisfying $E_P(Y \mid R, W) = \Pi(P)(R, W)m(P)(W) + \theta(P)(W)$ for some unspecified functions $m(P), \theta(P)$, and $\Pi(P)(R, W) = E_P(A \mid R, W)$.

Causal parameter: Let $\{am_\beta(v) : \beta\}$ be a working modeln for $E_0(Y(a) - Y(0) \mid V)$. We define our target parameter as a projection of the true $E_0(Y(a) - Y(0) \mid V) = aE_0(m_0(W) \mid V)$ on this working model. Specifically, given some weight function $h(A, V)$, let

$$\begin{aligned}
\beta_0 &= \arg\min_\beta E_0 \sum_a h(a, V)\{aE(m_0(W) \mid V) - am_\beta(V)\}^2 \\
&= \arg\min_\beta E_0 \sum_a h(a, V)a^2\{E(m_0(W) \mid V) - m_\beta(V)\}^2 \\
&= \arg\min_\beta E_0 \sum_a h(a, V)a^2\{m_0(W) - m_\beta(V)\}^2 \\
&\equiv \arg\min_\beta E_0 h_1(V)\{m_0(W) - m_\beta(V)\}^2,
\end{aligned}$$

where we defined $h_1(V) \equiv \sum_a h(a, V)a^2$.

For example, if V is empty, and $m_\beta(v) = \beta$, then $\beta_0 a = E_0(Y(a) - Y(0))$. We can also select $V = W$ and $m_\beta(w) = \beta w$, in which case $\beta_0 w$ is the projection of $m_0(w)$ on this linear working model $\{\beta W : \beta\}$.

Statistical Target parameter: Our target parameter is $\psi_0 = \beta_0$. We note that $\Psi(P_0) = \Psi(m_0, P_{W,0})$ only depends on P_0 through m_0 and $P_{W,0}$, while m_0, as statistical parameter of P_0, is identified as a function of $\bar{Q}_0 = E_0(Y \mid R, W)$ under the semiparametric regression model $\bar{Q}_0 = E_0(Y \mid R, W) = \pi_0(R, W)m_0(W) + \theta_0(W)$. We will also use notation $\Psi(\bar{Q}_0, P_{W,0})$ or $\Psi(\pi_0, m_0, \theta_0, P_{W,0})$.

Let $\Psi : \mathcal{M} \to \mathbb{R}^d$ be the target parameter mapping so that $\Psi(P_0) = \beta_0$, which exists under the identifiability assumptions stated in Lemma 1. The mapping $P \to \Psi(P)$ is defined by first evaluating $\Pi(P)$, then minimizing the squared-error risk $E_0(Y - \Pi(P)m(W) - \theta(W))^2$ over the semiparametric model $\Pi(P)(W)m(W) + \theta(W)$ with m, θ unspecified, resulting in $m(P)$, and finally, evaluating $\Psi(P) = \Psi(m(P), P_W)$.

The statistical estimation problem is now defined. We observe n i.i.d. copies of $O = (W, R, A, Y) \sim P_0 \in \mathcal{M}$, and we want to estimate $\psi_0 = \Psi(P_0)$ defined in terms of the mapping $\Psi : \mathcal{M} \to \mathbb{R}^d$.

3. Efficient influence curve of target parameter

We determine the efficient influence curve of $\Psi : \mathcal{M} \to \mathbb{R}^d$ in a two step process. Firstly, we determine the efficient influence curve in the model in which Π_0 is assumed to be known. Subsequently, we compute the correction term that yields the efficient influence curve in our model of interest in which Π_0 is unspecified.

3.1 Efficient influence curve in model in which Π_0 is known.

First, we consider the statistical model $\mathcal{M}(\pi_0) \subset \mathcal{M}$ in which $\Pi_0(R,W) = E_0(A \mid R,W)$ is known. For the sake of the derivation of the canonical gradient, let $W \in \mathbb{R}^N$ be discrete with support $\mathcal{W}$ so that we can view our model as a high dimensional parametric model, allowing us to re-use previously established results. That is, we represent the semiparametric regression model as $E_0(Y \mid R,W) = \Pi_0(R,W)\sum_w m_0(w)I(W=w) + \theta_0(W)$ so that it corresponds with a linear regression $f_{m_0}(R,W) = \Pi_0(R,W)\sum_w m_0(w)I(W=w)$ in which m_0 represents the coefficient vector. Define the N-dimensional vector $h(\Pi_0)(R,W) = d/dm_0 f_{m_0}(R,W) = (\Pi_0(R,W)I(W=w) : w \in \mathcal{W})$. By previous results on the semiparametric regression model, a gradient for the N-dimensional parameter $m(P)$ at $P = P_0 \in \mathcal{M}(\pi_0)$ is given by

$$D^*_{m,\Pi_0}(P_0) = C(\pi_0)^{-1}(h(\Pi_0)(R,W) - E(h(\Pi_0)(R,W) \mid W))(Y - f_{m_0}(R,W) - \theta_0(W)),$$

where $C(\pi_0)$ is a $N \times N$ matrix defined as

$$\begin{aligned} C(\pi_0) &= E_0\{d/dm_0 f_{m_0}(R,W) - E_0(d/dm_0 f_{m_0}(R,W) \mid W)\}^2 \\ &= E_0\{(I(W=w)\{\Pi_0(R,W) - E_0(\Pi_0(R,W) \mid W\} : w\}^2 \\ &= \text{Diag}\left(E_0\{I(W=w)\{\Pi_0(R,w) - E_0(\Pi_0(R,W) \mid W=w)\}^2\} : w\right) \\ &= \text{Diag}\left(P_{W,0}(w)E_0\left(\{\Pi_0(R,W) - E_0(\Pi_0(R,W) \mid W)\}^2 \mid W=w\right) : w\right). \end{aligned}$$

For notational convenience, given a vector X, we used notation X^2 for the matrix $XX^\top$. We also used the notation $\text{Diag}(x)$ for the $N \times N$ diagonal matrix with diagonal elements defined by vector x. Thus, the inverse of $C(\pi_0)$ exists in closed form and is given by:

$$C(\pi_0)^{-1} = \text{Diag}\left(\frac{1}{P_{W,0}(w)E_0(\{\Pi_0(R,W) - E_0(\Pi_0(R,W) \mid W)\}^2 \mid W=w)} : w\right).$$

This yields the following formula for the efficient influence curve of m_0 in model $\mathcal{M}(\pi_0)$:

$$\begin{aligned} &D^*_{m,\Pi_0,w}(P_0) = \tfrac{1}{P_{W,0}(w)E_0(\{\Pi_0(R,W) - E_0(\Pi_0(R,W)|W)\}^2|W=w)} \\ &I(W=w)(\Pi_0(R,W) - E_0(\Pi_0(R,W) \mid W))(Y - \Pi_0(R,W)m_0(W) - \theta_0(W)), \end{aligned}$$

where $D^*_{m,\Pi_0}(P_0)$ is $N \times 1$ vector with components $D^*_{m_0,\Pi_0,w}(P_0)$ indexed by $w \in \mathcal{W}$. We can further simplify this as follows:

$$\begin{aligned} &D^*_{m,\Pi_0,w}(P_0)(W,R,Y) = \tfrac{1}{P_{W,0}(w)E_0(\{\Pi_0(R,W) - E_0(\Pi_0(R,W)|W)\}^2|W=w)} \\ &I(W=w)(\Pi_0(R,w) - E_0(\Pi_0(R,W) \mid W=w))(Y - \Pi_0(R,w)m_0(w) - \theta_0(w)). \end{aligned}$$

This gradient equals the canonical gradient of m_0 in this model $\mathcal{M}(\pi_0)$, if $E_0((Y - E_0(Y \mid \Pi_0, W))^2 \mid R, W)$ is only a function of W. For example, this would hold if $E(U_Y^2 \mid R, W) = E_0(U_Y^2 \mid W)$. This might be a reasonable assumption for an instrumental variable R. The general formula for the canonical gradient is given in [**?**]. For the sake of presentation, we work with this gradient due to its relative simplicity. and the fact that it still equals the actual canonical gradient under this assumption.

We have that $\psi_0 = \phi(m_0, P_{W,0})$ for a mapping

$$\phi(m_0.P_{W,0}) = \arg\min_\beta E_0 \sum_a h(a,V) a^2 \left(m_0(W) - m_\beta(V)\right)^2,$$

defined by working model $\{m_\beta : \beta\}$. Let $d\phi(m_0, P_{W,0})(h_m, h_W) = \frac{d}{dm_0}\phi(m_0, P_{W,0})(h_m) + \frac{d}{dP_{W,0}}\phi(m_0, P_{W,0})(h_W)$ be the directional derivative in direction (h_m, h_W). The gradient of $\Psi : \mathcal{M}(\Pi_0) \rightarrow \mathbb{R}^d$ is given by $D^*_{\psi,\Pi_0}(P_0) = \frac{d}{dm_0}\phi(m_0, P_{W,0}) D^*_{m,\Pi_0}(P_0) + \frac{d}{dP_{W,0}}\phi(m_0, P_{W,0}) IC_W$, where $IC_W(O) = (I(W = w) - P_{W,0}(w) : w)$. We note that $\beta_0 = \phi(m_0, P_{W,0})$ solves the following $d \times 1$ equation

$$U(\beta_0, m_0, P_{W,0}) \equiv E_0 \sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V)(m_0(W) - m_{\beta_0}(V)) = 0.$$

By the implicit function theorem, the directional derivative of $\beta_0 = \phi(m_0, P_{W,0})$ is given by

$$\begin{array}{l} d\phi(m_0, P_{W,0})(h_m, h_W) = -\left\{\frac{d}{d\beta_0} U(\beta_0, m_0, P_{W,0})\right\}^{-1} \\ \left\{\frac{d}{dm_0} U(\beta_0, m_0, P_{W,0})(h_m) + \frac{d}{dP_{W,0}} U(\beta_0, m_0, P_{W,0})(h_W)\right\}. \end{array}$$

We need to apply this directional derivative to $(h_m, h_W) = (D^*_{m,\Pi_0}(P_0), IC_W)$. Recall we assumed that m_β is linear in β. We have

$$c_0 \equiv -\frac{d}{d\beta_0} U(\beta_0, m_0) = E_0 \sum_a h(a,V) a^2 \left\{\frac{d}{d\beta_0} m_{\beta_0}(V)\right\}^2,$$

which is a $d \times d$ matrix. Note that if $m_\beta(V) = \sum_j \beta_j V_j$, then this reduces to

$$c_0 = E_0 \sum_a h(a,V) a^2 \vec{V} \vec{V}^\top,$$

where $\vec{V} = (V_1, \ldots, V_d)$. We have

$$\frac{d}{dP_{W,0}} U(\beta_0, m_0, P_{W,0})(h_W) = \sum_w h_W(w) \sum_a h(a,v) a^2 \frac{d}{d\beta_0} m_{\beta_0}(v)(m_0(w) - m_{\beta_0}(v)).$$

Thus, the latter expression applied to $IC_W(O)$ yields $c_0^{-1} D^*_W(P_0)$, where

$$D^*_W(P_0) \equiv \sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V)(m_0(W) - m_{\beta_0}(V)).$$

In addition, the directional derivative $\frac{d}{d\epsilon} U(\beta_0, m_0 + \epsilon h_m, P_{W,0})|_{\epsilon=0}$ in the direction of the function h_m is given by

$$\frac{d}{dm_0} U(\beta_0, m_0, P_{W,0})(h_m) = E_0 \sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V) h_m(W).$$

We conclude that

$$d\phi(m_0, P_{W,0})(h_m, h_W) = D^*_W(P_0) + c_0^{-1} \left\{ E_0 \sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V) D^*_{m,W}(P_0) \right\}.$$

We conclude that the canonical gradient of $\Psi : \mathcal{M}(\Pi_0) \rightarrow \mathbb{R}^d$ is given by

$$\begin{aligned}
&D^*_{\psi,\Pi_0}(P_0)(O) = D^*_W(P_0)(O) \\
&+c_0^{-1} E_0 \textstyle\sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V) D^*_{m,W}(P_0) \\
&= c_0^{-1} \textstyle\sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V)(m_0(W) - m_{\beta_0}(V)) \\
&+c_0^{-1} \textstyle\sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V) \frac{1}{E_0(\{\Pi_0(R,W) - E(\Pi_0(R,W)|W)\}^2|W)} \\
&(\Pi_0(R,W) - E_0(\Pi_0(R,W) \mid W))(Y - \Pi_0(R,W) m_0(W) - \theta_0(W)).
\end{aligned}$$

We state this result in the following lemma and also state a robustness result for this efficient influence curve.

Lemma 2 *The efficient influence curve of $\Psi : \mathcal{M}(\Pi_0) \rightarrow \mathbb{R}^d$ is given by*

$$\begin{aligned}
&D^*_{\psi,\Pi_0}(P_0) = c_0^{-1} \textstyle\sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V)(m_0(W) - m_{\beta_0}(V)) \\
&+c_0^{-1} \textstyle\sum_a h(a,V) a^2 \frac{d}{d\beta_0} m_{\beta_0}(V) \frac{1}{E_0(\{\Pi_0(R,W) - E(\Pi_0(R,W)|W)\}^2|W)} \\
&(\Pi_0(R,W) - E_0(\Pi_0(R,W) \mid W))(Y - \Pi_0(R,W) m_0(W) - \theta_0(W)).
\end{aligned}$$

Assume the linear model $m_\beta(V) = \beta \vec{V}$. Let $h_1(V) = \sum_a h(a,V) a^2 \vec{V}$. We have that for all θ,

$$P_0 D^*_{\psi,\Pi_0}(g_0, m, \theta) = 0 \text{ if } E_0 h_1(V)(m - m_0)(W) = 0,$$

or, equivalently, if $\psi \equiv \Psi(m, P_{W,0}) = \Psi(m_0, P_{W,0}) = \psi_0$.

If we represent $D^*_{\psi,\Pi_0}(g_0, m, \theta, \psi)$ as an estimating function in ψ, then it follows that

$$P_0 D^*_{\psi,\Pi_0}(g_0, m, \theta, \psi) = c_0^{-1} P_0 h_1(V)(m_0(W) - \psi V),$$

so that $P_0 D^*_{\psi,\Pi_0}(g_0, m, \theta, \psi) = 0$ implies $\psi = \psi_0$. In other words, the efficient influence curve yields an unbiased estimating function for ψ_0 at correctly specified g_0, Π_0, but possibly misspecified m.

3.2 Canonical gradient in model in which Π_0 is unknown

We will now derive the efficient influence curve in model $\mathcal{M}$ in which Π_0 is unknown, which is obtained by adding a correction term $D_\pi(P_0)$ to the above derived $D^*_{\psi,\Pi_0}(P_0)$. The correction term $D_\pi(P_0)$ that needs to be added to D^*_{ψ,Π_0} is the influence curve of $P_0\{D^*_{\psi,\Pi_0}(\pi_n) - D^*_{\psi,\Pi_0}(\pi_0)\}$, where $D^*_{\psi,\Pi_0}(\pi) = D^*_{\psi,\Pi_0}(\beta_0, \theta_0, m_0, g_0, \pi)$ is the efficient influence curve in model $\mathcal{M}(\pi_0)$, as derived above with π_0 replaced by π, and π_n is the nonparametric NPMLE of π_0. Let $h_1(V) \equiv \sum_a h(a,v)a^2 \frac{d}{d\beta_0} m_{\beta_0}(v)$. Let $\pi(\epsilon) = \pi + \epsilon\eta$. We plug in for η the influence curve of the NPMLE $\Pi_n(r,w)$, which is given by

$$\eta(r,w) = \frac{I(R=r, W=w)}{P_0(r,w)}(A - \Pi(R,W)).$$

We have

$$\begin{aligned} D_\pi(P_0) &= \left. \tfrac{d}{d\epsilon} P_0 D^*_\psi(\pi(\epsilon)) \right|_{\epsilon=0} \\ &= P_0 c_0^{-1} h_1(V) \left\{ -2 \tfrac{E_0((\pi - E(\pi|W))(\eta - E(\eta|W))|W)}{E_0((\pi-E(\pi|W))^2|W)} \right. \\ &\qquad \left. (\pi - E(\pi \mid W)(Y - \pi m_0 - \theta_0) \right\} \\ &+ P_0 c_0^{-1} h_1(V) \left\{ \tfrac{(\eta - E(\eta|W))(Y - \pi m_0 - \theta_0)}{E_0((\pi - E(\pi|W))^2|W)} \right\} \\ &- P_0 c_0^{-1} h_1(V) \left\{ \tfrac{(\pi - E(\pi|W))\eta m_0}{E_0((\pi - E(\pi|W))^2|W)} \right\}. \end{aligned}$$

By writing the expectation w.r.t. P_0 as an expectation of a conditional expectation, given R, W, and noting that $E(Y - \pi_0 m_0 - \theta_0 \mid R, W) = 0$, it follows that the first two terms equal zero. Thus,

$$D_\pi(P_0) = -P_0 c_0^{-1} h_1(V) \left\{ \tfrac{(\pi - E_0(\pi|W))\eta m_0}{E_0((\pi - E_0(\pi|W))^2|W)} \right\}.$$

This yields as correction term:

$$\begin{aligned} D_\pi(P_0) &= -(A - \Pi_0(R,W)) \textstyle\int_{r,w} P_0(r,w) c_0^{-1} h_1(V) \left\{ \dfrac{(\pi - E(\pi|W)) \frac{I(R=r,W=w)}{P_0(r,w)} m_0}{E_0((\pi - E(\pi|W))^2|W)} \right\} \\ &= -(A - \Pi_0(R,W)) c_0^{-1} h_1(V) \left\{ \tfrac{(\pi(R,W) - E(\pi(R,W)|W)) m_0(W)}{E_0((\pi(R,W) - E_0(\pi(R,W)|W))^2|W)} \right\}. \end{aligned}$$

This proves the following lemma.

Lemma 3 *The efficient influence curve of* $\Psi : \mathcal{M} \to \mathbb{R}^d$ *is given by*

$$\begin{aligned} D^*(P_0) &= D^*_W(P_0) \\ &+ c_0^{-1} \tfrac{h_1(V)}{\sigma^2(g_0,\pi_0)(W)} (\pi_0(R,W) - E_0(\pi_0(R,W) \mid W))(Y - \pi_0(R,W) m_0(W) - \theta_0(W)) \\ &- c_0^{-1} \tfrac{h_1(V)}{\sigma^2(g_0,\pi_0)(W)} \{(\pi_0(R,W) - E_0(\pi_0(R,W) \mid W)) m_0(W)\} (A - \pi_0(R,W)) \\ &\equiv D^*_W(P_0) + C_Y(g_0,\pi_0)(R,W)(Y - \pi_0(R,W) m_0(W) - \theta_0(W)) \\ &\qquad - C_A(g_0,\pi_0,m_0)(A - \pi_0(R,W)) \\ &\equiv D^*_W(P_0) + D^*_Y(P_0) - D^*_A(P_0), \end{aligned}$$

where

$$\begin{aligned}
\sigma^2(g_0,\pi_0)(W) &= E_0(\{\Pi_0(R,W) - E(\Pi_0(R,W) \mid W)\}^2 \mid W) \\
h(g_0,\pi_0)(W) &= c_0^{-1}\frac{h_1(V)}{\sigma^2(g_0,\pi_0)(W)} \\
C_Y(g_0,\pi_0)(R,W) &= h(g_0,\pi_0)(W)(\pi_0(R,W) - E_{g_0}(\pi_0(R,W) \mid W)) \\
C_A(g_0,\pi_0,m_0)(R,W) &= C_Y(g_0,\pi_0)(R,W)m_0(W).
\end{aligned}$$

Double robustness of efficient influence curve: We already showed $P_0D^*(\pi_0,g_0,m,\theta) = 0$ if $\phi(m,P_{W,0}) = \phi(m_0,P_{W,0})$. If $\phi(m,P_{W,0}) = \phi(m_0,P_{W,0})$ (i.e., $\psi = \psi_0$), then,

$$P_0D^*(\pi,g_0,m,\theta) = P_0\frac{h_1}{\sigma^2(g_0,\pi)}(\pi - P_{g_0}\pi)(\pi_0 - \pi)(m_0 - m),$$

where we used notation $P_{g_0}h = E_{g_0}(h(R,W) \mid W)$ for the conditional expectation operator over R, given W. In fact,

$$\begin{aligned}
P_0D^*(\pi,g_0,m,\theta) &= P_0\frac{h_1}{\sigma^2(g_0,\pi)}(\pi - P_{g_0}\pi)(\pi_0 - \pi)(m_0 - m) \\
&\quad +\phi(m,P_{W,0}) - \phi(m_0,P_{W,0}),
\end{aligned}$$

This is thus second order in $(m - m_0)(\pi - \pi_0)$. In particular, it equals zero if $m = m_0$ or $\pi = \pi_0$, and $\psi = \psi_0$. We can thus also state the following double robustness result: if $m = m_0$, then $P_0D^*(\pi,g,m_0,\theta) = 0$ if $g = g_0$ or if $\pi = \pi_0$.

Double robustness of TMLE: If we represent $D^*(\Pi_0,g_0,m,\theta,\psi)$ as an estimating function in ψ, then it follows that

$$P_0D^*(\Pi_0,g_0,m,\theta,\psi) = c_0^{-1}P_0h_1(V)(m_0(W) - \psi V),$$

so that $P_0D^*(\Pi_0,g_0,m,\theta,\psi) = 0$ implies $\psi = \psi_0$. In other words, the efficient influence curve yields an unbiased estimating function for ψ_0 at correctly specified g_0, Π_0, but possibly misspecified m. As a consequence, the TMLE will be consistent for ψ_0 if both g_0 and Π_0 are consistently estimated. It will also be consistent for ψ_0 if g_0 and m_0 are consistently estimated, or if Π_0 and m_0 are consistently estimated.

4. Targeted minimum loss based estimation

4.1 Squared error loss and linear fluctuations.

Let $L(\pi)(O) = (A - \pi(R,W))^2$ and $L_\pi(\bar{Q})(O) = (Y - \pi(R,W)m(W) - \theta(W))^2$ be the squared error loss functions for π_0 and $\bar{Q}_0 = \pi_0 m_0 + \theta_0$, respectively. Note that the latter loss function is indexed by π. Let $L_\pi(g)(O) = (\pi(R,W) - E_g(\pi(R,W) \mid W))^2 + (\pi(R,W)^2 - E(\pi^2(R,W) \mid W))^2$ be a loss function for $E_{g_0}(\pi(R,W) \mid W)$

and $E_{g_0}(\pi^2(R,W) \mid W)$, two parameters of g_0. Let π_n^0 be an initial estimator of π_0. Let $\bar{Q}_n^0$ be an initial estimator of $\bar{Q}_0$ based on loss function $L_{\pi_n^0}(\bar{Q})$. Let g_n^0 be an initial estimator of g_0, or the relevant part thereof, based on $L_{\pi_n^0}(g)$. We can now define the fluctuations $\pi_n^0(\epsilon_2)$, $\bar{Q}_n^0(\epsilon_1)$, defined by $\pi_n^0(\epsilon_2) = \pi_n^0 + \epsilon_2 C_A(g_n^0, \pi_n^0, m_n^0)$ and $\bar{Q}_n^0(\epsilon_1) = \bar{Q}_n^0 + \epsilon_1 C_Y(g_n^0, \pi_n^0)$. We note that these fluctuations $\bar{Q}(\epsilon) = \pi m_\epsilon + \theta_\epsilon$ stay within the semiparametric regression model for $\bar{Q}_0$. We fit $\epsilon = (\epsilon_1, \epsilon_2)$ with the minimum loss-based estimators $\epsilon_{2n}^0 = \arg\min_\epsilon P_n L(\pi_n^0(\epsilon))$ and $\epsilon_{1n}^0 = \arg\min_\epsilon P_n L_{\pi_n^0}(\bar{Q}_n^0(\epsilon))$. This results in updates $\bar{Q}_n^1 = \bar{Q}_n^0(\epsilon_{1n}^0)$ and $\pi_n^1 = \pi_n^0(\epsilon_{2n}^0)$. One can now re-estimate g_0 based on the updated loss $L_{\pi_n^1}(g)$, which results in an update g_n^1. The above procedure describes an updating process mapping $(\pi_n^0, g_n^0, \bar{Q}_n^0)$ into $(\pi_n^1, g_n^1, \bar{Q}_n^1)$. This process can be iterated till convergence. Let $\bar{Q}_n^*$ be the resulting final estimator of $\bar{Q}_0$. This corresponds with a m_n^* and θ_n^*. The TMLE of ψ_0 is now defined by the plug-in estimator $\psi_n^* = \phi(m_n^*, P_{W,n})$. The TMLE solves the efficient influence curve equation

$$P_n D^*(g_n^*, \pi_n^*, m_n^*, \theta_n^*) = 0.$$

If g_n^* consistently estimates g_0, and either m_n^* or π_n^* is consistent for their target m_0 and π_0, then, under regularity conditions, the TMLE ψ_n^* is asymptotically linear with an influence curve that can be approximated by $D^*(g_0, \pi, m, \theta)$, where π, m, θ are the limits of $\pi_n^*, m_n^*, \theta_n^*$. This would be an asymptotically correct or conservative influence curve if g_n^* and m_n^* are consistent. Therefore we propose to estimate the asymptotic covariance matrix of ψ_n^* with $\Sigma_n = \frac{1}{n}\sum_{i=1}^n \{D^*(g_n, \pi_n^*, m_n^*, \theta_n^*)(O_i)\}^2$, and statistical inference for confidence intervals and testing can be based on the asymptotically valid working model $\psi_n^* \sim N_d(\psi_0, \Sigma_n/n)$.

4.2 Squared error loss and logistic fluctuations.

Suppose that we know that $A \in [0,1]$ that $m_0 \in (a_1, b_1)$, and $\theta_0 \in (a_2, b_2)$.

- Let Π_n^0 be an initial estimator of Π_0. Let m_n^0, θ_n^0 be an initial estimator of m_0, θ_0 respecting the above mentioned bounds. We use the relations $m = a_1 + (b_1 - a_1)m^*$ and $\theta = a_2 + (b_2 - a_2)\theta^*$, where m^*, θ^* are functions of W that are in $(0,1)$. This defines corresponding $m_n^{*,0}$ and $\theta_n^{*,0}$ of m_0^* and θ_0^*, respectively. Let $L_\Pi(g)(O) = (\pi(R,W) - E_g(\pi(R,W) \mid W))^2 + (\pi(R,W)^2 - E(\pi^2(R,W) \mid W))^2$ be a loss function for $E_{g_0}(\pi(R,W) \mid W)$ and $E_{g_0}(\pi^2(R,W) \mid W)$, two parameters of g_0. Let g_n^0 be an initial estimators of these two parameters of g_0, where we are abusing notation. Let $k = 0$.

- As loss function for Π_0 we can use $L(\Pi)(O) = -A \log \Pi(R,W) - (1-A)\log(1 - \Pi(R,W))$, and as fluctation of Π_n^k, we can use $\text{Logit}\Pi_n^k(\epsilon_2) = \text{Logit}\Pi_n^k + \epsilon_2 C_A(g_n^k, \Pi_n^k, m_n^k)$.

- For a given Π, as loss function for $\bar{Q}_0 = (m_0, \theta_0)$ we use $L_\Pi(\bar{Q})(O) = (Y - \Pi(R,W)m(W) - \theta(W))^2$. We use as fluctuation of m_n^k:

$$m_n^k(\epsilon) = a_1 + (b_1 - a_1)m_n^{k,*}(\epsilon),$$

where

$$\text{Logit} m_n^{k,*}(\epsilon) = \text{Logit} m_n^{*,k} + \epsilon h_1^k.$$

As fluctuation of θ_n^k, we use

$$\theta_n^k(\epsilon) = a_2 + (b_2 - a_2)\theta_n^{*,k}(\epsilon),$$

where

$$\text{Logit}\theta_n^{k,*}(\epsilon) = \text{Logit}\theta_n^{*,k} + \epsilon h_2^k.$$

This defines a fluctuation

$$\bar{Q}_n^k(\epsilon) = \Pi_n^k m_n^k(\epsilon) + \theta_n^k(\epsilon).$$

The choice h_1, h_2 that defines this least favorable submodel through the initial estimator $\bar{Q}_n^k$ will be defined below.

- We have

$$\tfrac{d}{d\epsilon} L_{\Pi_n^k}(\bar{Q}_n^k(\epsilon) = \Pi_n^k m_n^{*,k}(1 - m_n^{*,k})(b_1 - a_1)h_1^k + (b_2 - a_2)\theta_n^{*,k}(1 - \theta_n^{k,*})h_2^k.$$

Recall that $C_Y(g, \pi)(R, W) = \Pi(R, W)C_{Y,1}(g, \Pi)(W) + C_{Y,2}(g, \Pi)(W)$ for specified functions $C_{Y,1}, C_{Y,2}$. Thus we need to select (h_1, h_2) so that

$$\begin{aligned} h_1 &= \tfrac{C_{Y,1}(g,\Pi)}{m^*(1-m^*)(b_1-a_1)} \\ h_2 &= \tfrac{C_{Y,2}(g,\Pi)}{\theta^*(1-\theta^*)(b_2-a_2)}. \end{aligned}$$

Thus,

$$\begin{aligned} h_1^k &= \tfrac{C_{Y,1}(g_n^k,\Pi_n^k)}{m_n^{*,k}(1-m_n^{*,k})(b_1-a_1)} \\ h_2^k &= \tfrac{C_{Y,2}(g_n^k,\Pi_n^k)}{\theta_n^{*,k}(1-\theta_n^{*,k})(b_2-a_2)}. \end{aligned}$$

With this choice, we have that

$$\frac{d}{d\epsilon} L_\Pi(\bar{Q}(\epsilon))\Big|_{\epsilon=0} = C_Y(g, \Pi)(Y - \bar{Q}(R, W)).$$

- We note that these fluctuations $\bar{Q}(\epsilon) = \pi m_\epsilon + \theta_\epsilon$ stay within the semiparametric regression model for $\bar{Q}_0$. We fit $\epsilon = (\epsilon_1, \epsilon)$ with the minimum loss-based estimators $\epsilon_{1,n}^k = \arg\min_\epsilon P_n L(\Pi_n^k(\epsilon))$ and $\epsilon_n^k = \arg\min_\epsilon P_n L_{\Pi_n^k}(\bar{Q}_n^k(\epsilon))$. This results in updates $\bar{Q}_n^{k+1} = \bar{Q}_n^k(\epsilon_n^k)$ and $\Pi_n^{k+1} = \Pi_n^k(\epsilon_{1,n}^k)$. One can now re-estimate g_0 based on the updated loss $L_{\Pi_n^k}(g)$, which results in an update g_n^k. The above procedure describes an updating process mapping $(\Pi_n^k, g_n^k, \bar{Q}_n^k)$ into $(\pi_n^{k+1}, g_n^{k+1}, \bar{Q}_n^{k+1})$. This process can be iterated till convergence: i.e., set $k = k + 1$, repeat the above updating process till convergence defined by $\epsilon_n^k \approx 0$.

- Let $\bar{Q}_n^*$ be the resulting final estimator of $\bar{Q}_0$. This corresponds with targeted estimators m_n^* and θ_n^* of m_0 and θ_0, respectively. The TMLE of ψ_0 is now defined by the plug-in estimator $\psi_n^* = \phi(m_n^*, P_{W,n})$.

By construction the TMLE solves the efficient influence curve equation

$$P_n D^*(g_n^*, \pi_n^*, m_n^*, \theta_n^*) = 0.$$

If g_n^* consistently estimates g_0, and either m_n^* or π_n^* is consistent for their target m_0 and π_0, then, under regularity conditions, the TMLE ψ_n^* is asymptotically linear with an influence curve that can be approximated by $D^*(g_0, \pi, m, \theta)$, where π, m, θ are the limits of $\pi_n^*, m_n^*, \theta_n^*$. This would be an asymptotically correct or conservative influence curve if g_n^* and m_n^* are consistent. Therefore we propose to estimate the asymptotic covariance matrix of ψ_n^* with $\Sigma_n = \frac{1}{n}\sum_{i=1}^n \{D^*(g_n, \pi_n^*, m_n^*, \theta_n^*)(O_i)\}^2$, and statistical inference for confidence intervals and testing can be based on the asymptotically valid working model $\psi_n^* \sim N_d(\psi_0, \Sigma_n/n)$.

5. Efficient influence curve of target parameter when assuming a parametric form for effect of treatment as function of covariates

We now assume $m_0 = m_{\alpha_0}$ for some model $\{m_\alpha : \alpha\}$, which implies the semiparametric regression model $E_0(Y \mid R, W) = \Pi_0(R, W) m_{\beta_0}(W) + \theta_0(W)$. Let $f_\beta(R, W) = \Pi_0(R, W) m_\beta(W)$. Let $m_\alpha(W) = \alpha^\top W^*$, where W^* is k-dimensional vector of functions of W. Note that α is d-dimensional and $\frac{d}{d\alpha} m_\alpha(W) = W^*$.

5.1 Efficient influence curve in model in which Π_0 is known.

First, we consider the statistical model $\mathcal{M}(\pi_0) \subset \mathcal{M}$ in which $\Pi_0(R, W) = E_0(A \mid R, W)$ is known. Define the k-dimensional vector

$$h(\Pi_0)(R, W) = d/\alpha_0 m_{\alpha_0}(R, W) = \Pi_0(R, W) d/d\alpha_0 m_{\alpha_0}(W) = \Pi_0(R, W) W^*.$$

By previous results on the semiparametric regression model, a gradient for the k-dimensional parameter $\alpha(P)$ at $P = P_0 \in \mathcal{M}(\pi_0)$ is given by

$$D^*_{\alpha,\Pi_0}(P_0) = C(\pi_0)^{-1}(h(\Pi_0)(R, W) - E(h(\Pi_0)(R, W) \mid W))(Y - f_{\alpha_0}(R, W) - \theta_0(W)),$$

where $C(\pi_0)$ is a $k \times k$ matrix defined as

$$\begin{aligned} C(\pi_0) &= E_0\{d/d\alpha_0 f_{\alpha_0}(R, W) - E_0(d/d\alpha_0 f_{\alpha_0}(R, W) \mid W)\}^2 \\ &= E_0\{(W^* W^{*\top}\{\Pi_0(R, W) - E_0(\Pi_0(R, W) \mid W\}^2\}. \end{aligned}$$

Let $C(\pi_0)^{-1}$ be the inverse of $C(\pi_0)$.

This gradient equals the canonical gradient of α_0 in this model $\mathcal{M}(\pi_0)$, if $E_0((Y - E_0(Y \mid \Pi_0, W))^2 \mid R, W)$ is only a function of W. For example, this would hold if

$E(U_Y^2 \mid R, W) = E_0(U_Y^2 \mid W)$. This might be a reasonable assumption for an instrumental variable R. The general formula for the canonical gradient is given in [**?**]. For the sake of presentation, we work with this gradient due to its relative simplicity. and the fact that it still equals the actual canonical gradient under this assumption.

We have that $\psi_0 = \phi(\alpha_0, P_{W,0})$ for a mapping

$$\phi(\alpha_0.P_{W,0}) = \arg\min_{\beta} E_0 \sum_a h(a,V)a^2 \left(m_{\alpha_0}(W) - m_\beta(V)\right)^2 ,$$

defined by working model $\{m_\beta : \beta\}$. Let $d\phi(\alpha_0, P_{W,0})(h_\alpha, h_W) = \frac{d}{d\alpha_0}\phi(\alpha_0, P_{W,0})(h_\alpha) + \frac{d}{dP_{W,0}}\phi(\alpha_0, P_{W,0})(h_W)$ be the directional derivative in direction (h_β, h_W). The gradient of $\Psi : \mathcal{M}(\Pi_0) \rightarrow \mathbb{R}^d$ is given by $D^*_{\alpha,\Pi_0}(P_0) = \frac{d}{d\alpha_0}\phi(\alpha_0, P_{W,0}) D^*_{\alpha,\Pi_0}(P_0) + \frac{d}{dP_{W,0}}\phi(\alpha_0, P_{W,0}) IC_W$, where $IC_W(O) = (I(W = w) - P_{W,0}(w) : w)$ is the influence curve of the empirical distribution of W. We note that $\beta_0 = \phi(\alpha_0, P_{W,0})$ solves the following $d \times 1$ equation

$$U(\beta_0, \alpha_0, P_{W,0}) \equiv E_0 \sum_a h(a,V)a^2 \frac{d}{d\beta_0} m_{\beta_0}(V)(m_{\alpha_0}(W) - m_{\beta_0}(V)) = 0.$$

By the implicit function theorem, the directional derivative of $\beta_0 = \phi(\alpha_0, P_{W,0})$ is given by

$$d\phi(\alpha_0, P_{W,0})(h_\alpha, h_W) = -\left\{\frac{d}{d\beta_0}U(\beta_0, \alpha_0, P_{W,0})\right\}^{-1} \left\{\frac{d}{d\alpha_0}U(\beta_0, \alpha_0, P_{W,0})(h_\alpha) + \frac{d}{dP_{W,0}}U(\beta_0, \alpha_0, P_{W,0})(h_W)\right\}.$$

We need to apply this directional derivative to $(h_\alpha, h_W) = (D^*_{\alpha,\Pi_0}(P_0), IC_W)$. Recall we assumed that m_β is linear in β. We have

$$c_0 \equiv -\frac{d}{d\beta_0}U(\beta_0, \alpha_0, P_{W,0}) = E_0 \sum_a h(a,V)a^2 \left\{\frac{d}{d\beta_0} m_{\beta_0}(V)\right\}^2 ,$$

which is a $d \times d$ matrix. Note that if $m_\beta(V) = \sum_j \beta_j V_j$, then this reduces to

$$c_0 = E_0 \sum_a h(a,V)a^2 \vec{V}\vec{V}^\top ,$$

where $\vec{V} = (V_1, \ldots, V_d)$. We have

$$\frac{d}{dP_{W,0}}U(\beta_0, \alpha_0, P_{W,0})(h_W) = \sum_w h_W(w) \sum_a h(a,v)a^2 \frac{d}{d\beta_0} m_{\beta_0}(v)(m_{\alpha_0}(w) - m_{\beta_0}(v)).$$

Thus, the latter expression applied to $IC_W(O)$ yields the contribution $c_0^{-1} D^*_W(P_0)$, where

$$D^*_W(P_0) \equiv \sum_a h(a,V)a^2 \frac{d}{d\beta_0} m_{\beta_0}(V)(m_{\alpha_0}(W) - m_{\beta_0}(V)).$$

In addition,

$$\frac{d}{d\alpha_0}U(\beta_0,\alpha_0,P_{W,0}) = E_0\sum_a h(a,V)a^2\frac{d}{d\beta_0}m_{\beta_0}(V)\frac{d}{d\alpha_0}m_{\alpha_0}(W).$$

We conclude that

$$d\phi(\alpha_0,P_{W,0})(h_\alpha,h_W) = \\ D^*_W(P_0) + c_0^{-1}\left\{E_0\textstyle\sum_a h(a,V)a^2\frac{d}{d\beta_0}m_{\beta_0}(V)\frac{d}{d\alpha_0}m_{\alpha_0}(W)D^*_{\alpha,\Pi_0}(P_0)\right\}.$$

We conclude that the canonical gradient of $\Psi:\mathcal{M}(\Pi_0)\rightarrow \mathbb{R}^d$ is given by

$$\begin{aligned} D^*_{\psi,\Pi_0}(P_0) &= D^*_W(P_0)(O) \\ &\quad + c_0^{-1}\left\{E_0\sum_a h(a,V)a^2\frac{d}{d\beta_0}m_{\beta_0}(V)\frac{d}{d\alpha_0}m_{\alpha_0}(W)\right\}D^*_{\alpha,\Pi_0}(P_0)(O) \\ &= D^*_W(P_0)(O) + \\ &\quad c_0^{-1}\left\{E_0h_1(V)\vec{V}\vec{W}^{*\top}\right\}C(\pi_0)^{-1}(h(\Pi_0)(R,W)-E(h(\Pi_0)(R,W)\mid W))\times \\ &\quad (Y-f_{\alpha_0}(R,W)-\theta_0(W)). \end{aligned}$$

We state this result in the following lemma and also state a robustness result for this efficient influence curve.

Lemma 4 *Let* $h_1(V)=\sum_a h(a,V)a^2\vec{V}$*.The efficient influence curve of* $\Psi:\mathcal{M}(\Pi_0)\rightarrow \mathbb{R}^d$ *is given by*

$$D^*_{\psi,\Pi_0}(P_0) = c_0^{-1}h_1(V)\tfrac{d}{d\beta_0}m_{\beta_0}(V)(m_{\alpha_0}(W)-m_{\beta_0}(V)) \\ +c_0^{-1}\left\{E_0h_1(V)\vec{V}\vec{W}^{*\top}\right\}C(\pi_0)^{-1}(h(\Pi_0)(R,W)-E(h(\Pi_0)(R,W)\mid W))\times \\ (Y-f_{\alpha_0}(R,W)-\theta_0(W)).$$

We have that

$$P_0D^*_{\psi,\Pi_0}(g,m_{\alpha_0},\theta)=0, \text{ if either } g=g_0 \text{ or } \theta=\theta_0.$$

5.2 Canonical gradient in model in which Π_0 is unknown

We will now derive the efficient influence curve in model $\mathcal{M}$ in which Π_0 is unknown, which is obtained by adding a correction term $D_\pi(P_0)$ to the above derived $D^*_{\psi,\Pi_0}(P_0)$. The correction term $D_\pi(P_0)$ that needs to be added to D^*_{ψ,Π_0} is the influence curve of $P_0\{D^*_{\psi,\Pi_0}(\pi_n)-D^*_{\psi,\Pi_0}(\pi_0)\}$, where $D^*_{\psi,\Pi_0}(\pi)=D^*_{\psi,\Pi_0}(\beta_0,\theta_0,\alpha_0,g_0,\pi)$ is the efficient influence curve in model $\mathcal{M}(\pi_0)$, as derived above with π_0 replaced by π, and π_n is the nonparametric NPMLE of π_0. Let $h_1(V)\equiv\sum_a h(a,v)a^2\frac{d}{d\beta_0}m_{\beta_0}(v)$. Let $\pi(\epsilon)=\pi+\epsilon\eta$. We plug in for η the influence curve of the NPMLE $\Pi_n(r,w)$, which is given by

$$\eta(r,w)=\frac{I(R=r,W=w)}{P_0(r,w)}(A-\Pi(R,W)).$$

We have

$$\begin{aligned} D_\pi(P_0) &= \left. \frac{d}{d\epsilon} P_0 D^*_\psi(\pi(\epsilon)) \right|_{\epsilon=0} \\ &= -\left\{ P_0 c_0^{-1} h_1(V) \vec{V} W^{*\top} \right\} C(\pi_0)^{-1} P_0 \left\{ W^* W^{*\top} (\pi_0 - E(\pi_0 \mid W)) \eta(R,W) \right\}. \end{aligned}$$

This yields as correction term:

$$\begin{aligned} & D_\pi(P_0)(O) = -(A - \Pi_0(R,W)) \\ & \left\{ P_0 c_0^{-1} h_1(V) \vec{V} W^{*\top} \right\} C(\pi_0)^{-1} \left\{ W^* W^{*\top} (\pi_0(R,W) - E(\pi_0 \mid W)) \right\}. \end{aligned}$$

This proves the following lemma.

Lemma 5 *The efficient influence curve of* $\Psi : \mathcal{M} \rightarrow \mathbb{R}^d$ *is given by*

$$\begin{aligned} & D^*(P_0) = D^*_W(P_0) \\ & + c_0^{-1} \left\{ E_0 h_1(V) \vec{V} \vec{W}^{*\top} \right\} C(\pi_0)^{-1} W^* (\Pi_0 - E(\Pi_0(R,W) \mid W))(Y - f_{\alpha_0}(R,W) - \theta_0(W)) \\ & - \left\{ P_0 c_0^{-1} h_1(V) \vec{V} W^{*\top} \right\} C(\pi_0)^{-1} \left\{ W^* W^{*\top} (\pi_0(R,W) - E(\pi_0 \mid W)) \right\} (A - \Pi_0(R,W)) \\ & \equiv D^*_W(P_0) + C_Y(g_0,\pi_0)(R,W)(Y - \pi_0(R,W) m_{\alpha_0}(W) - \theta_0(W)) \\ & \qquad - C_A(g_0,\pi_0,m_0)(A - \pi_0(R,W)) \\ & \equiv D^*_W(P_0) + D^*_Y(P_0) - D^*_A(P_0), \end{aligned}$$

where

$$\begin{aligned} & C_Y(g_0,\pi_0)(R,W) = c_0^{-1} \left\{ E_0 \textstyle\sum_a h(a,V) a^2 \vec{V} \vec{W}^{*\top} \right\} \times \\ & \qquad C(\pi_0)^{-1} (h(\Pi_0)(R,W) - E(h(\Pi_0)(R,W) \mid W)) \\ & C_A(g_0,\pi_0,m_0)(R,W) = \left\{ P_0 c_0^{-1} h_1(V) \vec{V} W^{*\top} \right\} C(\pi_0)^{-1} \left\{ W^* W^{*\top} (\pi_0(R,W) - E(\pi_0 \mid W)) \right\}. \end{aligned}$$

Double robustness of efficient influence curve: We already showed $P_0 D^*(\pi_0, g, \alpha_0, \theta) = 0$ if $g = g_0$ or $\theta = \theta_0$. We also have that $P_0 D^*(\pi, g_0, \alpha_0, \theta) = 0$ for all θ and π.

The TMLE is analogue to the TMLE presented for the nonparametric model for $m_0(W)$.

6. Extension to structural equation for outcome that is non-linear in treatment.

Consider the structural equation model $Y = \sum_{j=1}^J A^j m_{j,0}(W) + \theta_0(W) + U_Y$, where the functions $m_{j,0}$, $j = 1, \ldots, J$, are unspecified, and $E(U_Y \mid R, W) = 0$. Under this assumption, we have the following semiparametric regression model:

$$E(Y \mid R, W) = \sum_{j=1}^J E_0(A^j \mid W) m_{j,0}(W) + \theta_0(W) \equiv \sum_{j=1}^J \Pi_{0,j}(W) m_{j,0}(W) + \theta_0(W),$$

where we defined $\Pi_{0,j}(W) = E_0(A^j \mid W)$. The counterfactuals are defined as $Y(a) = \sum_{j=1}^J a^j m_{j,0}(W) + \theta_0(W) + U_Y$, and $E_0(Y(a) - Y(0) \mid V) = \sum_{j=1}^J a^j E(m_{j,0}(W) \mid V)$.

Given a working model $\{m_\beta : \beta\}$, and weight function h, we can define the target parameter as

$$\beta_0 = \arg\min_\beta E_0 \sum_a \sum_v h(a,v)(\sum_j a^j E_0(m_{j,0}(W) \mid V=v) - m_\beta(a,v))^2.$$

Analogue to above, we can now compute the efficient influence curve, and develop the TMLE of $\beta_0 = \Phi((m_{j0} : j), P_{W,0})$.

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