Supporting Information for "Targeted Estimation and Inference for the Sample Average Treatment Effect in Trials With and Without Pair-Matching"

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Appendix A: The TMLE is an asymptotically linear estimator of the SATE in randomized trial without pair-matching

Consider the statistical parameter corresponding to the population average treatment effect (PATE):

$$\begin{aligned}\Psi^{\mathcal{P}}(P_0) &= E_0\big[E_0(Y|A=1,W) - E_0(Y|A=0,W)\big] \\ &= E_0\big[\bar{Q}_0(1,W) - \bar{Q}_0(0,W)\big]\end{aligned}$$

where $\bar{Q}_0(A,W) = E_0(Y|A,W)$ denotes the conditional expectation of the outcome, given the exposure and covariates. The TMLE for $\Psi^{\mathcal{P}}(P_0)$ is defined by the following substitution estimator:

$$\Psi_n(P_n) = \frac{1}{n}\sum_{i=1}^{n}\big[\bar{Q}_n^*(1,W_i) - \bar{Q}_n^*(0,W_i)\big]$$

where P_n denotes the empirical distribution, putting mass $1/n$ on each $O_i = (W_i, A_i, Y_i)$ and $\bar{Q}_n^*(A,W)$ denotes the targeted estimator.

Suppose the exposure mechanism, denoted $g_0(A|W) = P_0(A|W)$, is known as in a randomized trial. Under the following regularity conditions, the TMLE of $\Psi^{\mathcal{P}}(P_0)$ is asymptotically linear (van der Laan and Rubin, 2006):

$$\Psi_n(P_n) - \Psi^{\mathcal{P}}(P_0) = \frac{1}{n}\sum_{i=1}^{n} D^{\mathcal{P}}(\bar{Q}, g_0)(O_i) + o_P(1/\sqrt{n})$$

with influence curve

$$D^{\mathcal{P}}(\bar{Q}, g_0)(O) = \left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y - \bar{Q}(A,W)\big) + \bar{Q}(1,W) - \bar{Q}(0,W) - \Psi^{\mathcal{P}}(P_0)$$

where $\bar{Q}(A,W)$ denotes the limit of the TMLE $\bar{Q}_n^*(A,W)$. Specifically, we assume the positivity assumption holds: for some $\delta > 0$, $\delta < g_0(1|W) < 1-\delta$. We also assume that $P_0\big[D_n^{\mathcal{P}}(\bar{Q}_n^*, g_0) - D^{\mathcal{P}}(\bar{Q}, g_0)\big]^2 \to 0$ in probability and that $D_n^{\mathcal{P}}(\bar{Q}_n^*, g_0)$ is in the P_0-Donsker class with probability tending to 1. Here we used notation $P_0 f = \int f(o) dP_0(0)$ for some function f.

Theorem 1. *Suppose we have n i.i.d. observations of random variable $O = (W, A, Y) \sim P_0$, where W denotes the baseline covariates, A denotes the exposure, and Y denotes the outcome. Consider the sample average treatment effect (SATE) $\Psi^{\mathcal{S}}(P_{U,O}) = \frac{1}{n}\sum_{i=1}^{n} Y_i(1) - Y_i(0)$, where $P_{U,O}$ denotes the joint distribution of the background factors $U = (U_W, U_A, U_Y)$ and observed factors $O = (W, A, Y)$. Under the above regularity conditions, the TMLE $\Psi_n(P_n) = \frac{1}{n}\sum_{i=1}^{n} \bar{Q}_n^*(1, W_i) - \bar{Q}_n^*(0, W_i)$ is an asymptotically linear estimator of the SATE:*

$$\Psi_n(P_n) - \Psi^{\mathcal{S}}(P_{U,O}) = \frac{1}{n}\sum_{i=1}^{n} D^{\mathcal{S}}(\bar{Q}, \bar{Q}_0, g_0)(U_i, O_i) + o_P(1/\sqrt{n})$$

with influence curve

$$\begin{aligned} D^{\mathcal{S}}(\bar{Q},\bar{Q}_0,g_0)(U,O) &= D^C(\bar{Q},\bar{Q}_0,g_0)(O) - D^F(\bar{Q}_0)(U,O) \\ D^C(\bar{Q},\bar{Q}_0,g_0)(O) &= \left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y-\bar{Q}(A,W)\big) - \big[\bar{Q}_0(W)-\bar{Q}(W)\big] \\ D^F(\bar{Q}_0)(U,O) &= Y(1)-Y(0)-\bar{Q}_0(W) \end{aligned}$$

where $\bar{Q}(W) = \bar{Q}(1,W) - \bar{Q}(0,W)$ denotes the difference in the treatment-specific conditional means.

We note that D^C is the influence curve of the TMLE for the conditional estimand $\Psi^{\mathcal{C}}(P_0) = \frac{1}{n}\sum_{i=1}^n \bar{Q}_0(1,W_i) - \bar{Q}_0(0,W_i)$, which corresponds to the conditional average treatment effect (CATE) under the necessary causal assumptions (Balzer et al., 2015). The remaining non-identifiable piece D^F is difference between the unit-specific effect and the effect within strata of covariates.

Proof. Let $\bar{Q}_0(W) = \bar{Q}_0(1,W) - \bar{Q}_0(0,W)$ denote the true difference in treatment-specific means. We can write the deviation between the TMLE $\Psi_n(P_n)$ for the population estimand $\Psi^{\mathcal{P}}(P_0)$ and the SATE as

$$\begin{aligned} \Psi_n(P_n) - \Psi^{\mathcal{S}}(P_{U,O}) &= \Psi_n(P_n) - \Psi^{\mathcal{P}}(P_0) - \big[\Psi^{\mathcal{S}}(P_{U,O}) - \Psi^{\mathcal{P}}(P_0)\big] \\ &= \frac{1}{n}\sum_{i=1}^n D^{\mathcal{P}}(O_i) - \big[\Psi^{\mathcal{S}}(P_{U,O}) - \Psi^{\mathcal{P}}(P_0)\big] + o_P(1/\sqrt{n}) \\ &= \frac{1}{n}\sum_{i=1}^n D^{\mathcal{P}}(O_i) - \left[\frac{1}{n}\sum_{i=1}^n Y_i(1) - Y_i(0) - \bar{Q}_0(W_i) + \bar{Q}_0(W_i) - \Psi^{\mathcal{P}}(P_0)\right] + o_P(1/\sqrt{n}) \\ &= \frac{1}{n}\sum_{i=1}^n \left(\frac{\mathbb{I}(A_i=1)}{g_0(1|W_i)} - \frac{\mathbb{I}(A_i=0)}{g_0(0|W_i)}\right)\big(Y_i - \bar{Q}(A_i,W_i)\big) + \bar{Q}(W_i) - \Psi^{\mathcal{P}}(P_0) \\ &\quad - \left[\frac{1}{n}\sum_{i=1}^n Y_i(1) - Y_i(0) - \bar{Q}_0(W_i) + \bar{Q}_0(W_i) - \Psi^{\mathcal{P}}(P_0)\right] + o_P(1/\sqrt{n}) \\ &= \frac{1}{n}\sum_{i=1}^n \left(\frac{\mathbb{I}(A_i=1)}{g_0(1|W_i)} - \frac{\mathbb{I}(A_i=0)}{g_0(0|W_i)}\right)\big(Y_i - \bar{Q}(A_i,W_i)\big) - \big[\bar{Q}_0(W_i) - \bar{Q}(W_i)\big] \\ &\quad - \left[\frac{1}{n}\sum_{i=1}^n Y_i(1) - Y_i(0) - \bar{Q}_0(W_i)\right] + o_P(1/\sqrt{n}) \\ &= \frac{1}{n}\sum_{i=1}^n D^C(O_i) - D^F(U_i,O_i) + o_P(1/\sqrt{n}) \end{aligned}$$

where the influence curve of the TMLE for the conditional estimand $\Psi^{\mathcal{C}}(P_0)$ is

$$D^C(O) = \left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y-\bar{Q}(A,W)\big) - \big[\bar{Q}_0(W)-\bar{Q}(W)\big]$$

and where

$$D^F(U,O) = Y(1) - Y(0) - \big[\bar{Q}_0(1,W) - \bar{Q}_0(0,W)\big]$$

Thus, we have shown the TMLE is an asymptotically linear estimator of the SATE:

$$\Psi_n(P_n) - \Psi^{\mathcal{S}}(P_{U,O}) = \frac{1}{n}\sum_{i=1}^n D^{\mathcal{S}}(U_i,O_i) + o_P(1/\sqrt{n})$$

with influence curve

$$D^{\mathcal{S}}(U,O) = D^C(O) - D^F(U,O)$$

□

Strictly speaking, the influence curve must only be a function of the observed data O. Nonetheless, the theorem is sufficient to prove asymptotic normality and consistency of the TMLE for estimation and inference of the SATE.

Appendix A.1: Variance and variance estimation for the TMLE of the SATE in a randomized trial without pair-matching

Theorem 2. *The standardized TMLE for the SATE is asymptotically normal:*

$$\sqrt{n}\Big[\Psi_n(P_n) - \Psi^{\mathcal{S}}(P_{U,O})\Big] \xrightarrow{D} N(0, \sigma^{2,\mathcal{S}})$$
$$\text{with } \sigma^{2,\mathcal{S}} = Var[D^C] + Var[D^F] - 2Cov[D^C, D^F]$$
$$= Var[D^C] - Var[D^F]$$

Proof. The covariance term is

$$\begin{aligned} Cov[D^C, D^F] &= E\big[D^C \times D^F\big] \\ &= E\Bigg[\Bigg\{\left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y - \bar{Q}(A,W)\big) - \big(\bar{Q}_0(W) - \bar{Q}(W)\big)\Bigg\} \\ &\quad \times \big\{Y(1) - Y(0) - \bar{Q}_0(W)\big\}\Bigg] \\ &= E\Bigg[\left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y - \bar{Q}(A,W)\big) \times \big\{Y(1) - Y(0) - \bar{Q}_0(W)\big\}\Bigg] \\ &\quad - E\Big[\big\{\bar{Q}_0(W) - \bar{Q}(W)\big\} \times \big\{Y(1) - Y(0) - \bar{Q}_0(W)\big\}\Big] \end{aligned}$$

For the first term, we have

$$\begin{aligned} &E\Bigg[\left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y - \bar{Q}(A,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \\ &= E\Bigg[\left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y - \bar{Q}(A,W) + \bar{Q}_0(A,W) - \bar{Q}_0(A,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \\ &= E\Bigg[\left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(Y - \bar{Q}_0(A,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \\ &+ E\Bigg[\left(\frac{\mathbb{I}(A=1)}{g_0(1|W)} - \frac{\mathbb{I}(A=0)}{g_0(0|W)}\right)\big(\bar{Q}_0(A,W) - \bar{Q}(A,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \end{aligned}$$

It follow that this equals

$$\begin{aligned} &= E\Bigg[\frac{\mathbb{I}(A=1)}{g_0(1|W)}\big(Y(1) - \bar{Q}_0(1,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \\ &- E\Bigg[\frac{\mathbb{I}(A=0)}{g_0(0|W)}\big(Y(0) - \bar{Q}_0(0,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \\ &+ E\Bigg[\frac{\mathbb{I}(A=1)}{g_0(1|W)}\big(\bar{Q}_0(1,W) - \bar{Q}(1,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \\ &- E\Bigg[\frac{\mathbb{I}(A=0)}{g_0(0|W)}\big(\bar{Q}_0(0,W) - \bar{Q}(0,W)\big) \times \big[Y(1) - Y(0) - \bar{Q}_0(W)\big]\Bigg] \end{aligned}$$

Under the randomization assumption, we have

$$E\left[\frac{\mathbb{I}(A=a)}{g_0(a|W)}\middle|Y(1),Y(0),W\right]=1$$

Therefore, the sum of first two terms reduce to the variance of the D^F component

$$E\bigg[\big[Y(1)-Y(0)-\bar{Q}_0(W)\big]\times\big[Y(1)-Y(0)-\bar{Q}_0(W)\big]\bigg]=E\bigg[\big[Y(1)-Y(0)-\bar{Q}_0(W)\big]^2\bigg],$$

and the sum of the last two terms is

$$E\bigg[\big\{\bar{Q}_0(W)-\bar{Q}(W)\big\}\times\big\{Y(1)-Y(0)-\bar{Q}_0(W)\big\}\bigg].$$

Therefore, we have that the covariance term equals the variance of the non-identifiable component D^F:

$$Cov[D^C,D^F]=Var[D^F].$$

Thus, the asymptotic variance of the standardized estimator for the SATE is

$$\sigma^{2,\mathcal{S}}=Var[D^C]-Var[D^F].$$

□

The asymptotic variance of the standardized TMLE for the SATE $\sigma^{2,\mathcal{S}}$ is always less than or equal to the asymptotic variance of the standardized TMLE for the conditional parameter $\sigma^{2,\mathcal{C}}=Var[D^C]$. As shown in Balzer et al. (2015), we can estimate the upper bound

$$\hat{\sigma}^{2,\mathcal{S}}=\hat{\sigma}^{2,\mathcal{C}}=\frac{1}{n}\sum_{i=1}^{n}\left\{\hat{D}^{\mathcal{C}}(\bar{Q}_n^*,g_0)(O_i)\right\}^2$$

$$\text{where } \hat{D}^{\mathcal{C}}(\bar{Q}_n^*,g_0)(O_i)=\left(\frac{\mathbb{I}(A_i=1)}{g_0(1|W_i)}-\frac{\mathbb{I}(A_i=0)}{g_0(0|W_i)}\right)\big(Y_i-\bar{Q}_n^*(A_i,W_i)\big).$$

Appendix A.2: Generalization to allow for estimation of the exposure mechanism

Suppose our target of inference is the population estimand $\Psi^{\mathcal{P}}(P_0)$ and the exposure mechanism is consistently estimated with maximum likelihood: $g_n(A|W)$. Then the TMLE is asymptotically linear with influence curve given by the influence curve at the possibly misspecified limit $\bar{Q}(A,W)$ minus its projection on the tangent space T_g of the model for $g_0(A|W)$ (van der Laan and Robins, 2003):

$$D^{\mathcal{P},g_n}(\bar{Q},g_0)=D^{\mathcal{P}}(\bar{Q},g_0)-\prod\big[D^{\mathcal{P}}(\bar{Q},g_0)|T_g\big].$$

This projection is a function of (A,W) with conditional mean zero, given W. Analogously, when we target the conditional estimand $\Psi^{\mathcal{C}}(P_0)$, the influence curve of the TMLE is

$$D^{\mathcal{C},g_n}(\bar{Q},g_0)=D^{C}(\bar{Q},g_0)-\prod\big[D^{C}(\bar{Q},g_0)|T_g\big],$$

and when we target the SATE $\Psi^{\mathcal{S}}(P_{U,O})$, the influence curve of the TMLE is

$$D^{\mathcal{S},g_n}(\bar{Q},g_0)=D^{\mathcal{C},g_n}(\bar{Q},g_0)-D^F.$$

The proof is analogous to the above and thus omitted.

The standardized estimator of the SATE then is asymptotically normal with mean 0 and variance given by the variance of influence curve:

$$\sigma^{2,\mathcal{S},g_n} = Var[D^{\mathcal{C},g_n}] + Var[D^F] - 2Cov[D^{\mathcal{C},g_n}, D^F]$$

The covariance of the projection $\prod \left[D^C(\bar{Q}, g_0)\middle|T_g\right]$ and D^F is zero. (If we take the expectation given (A, W), then the projection term is constant and the D^F term is zero.) Thus, when the exposure mechanism is estimated according to a correctly specified model, the asymptotic variance of standardized estimator is

$$\sigma^{2,\mathcal{S},g_n} = Var[D^{\mathcal{C},g_n}] - Var[D^F].$$

We will have a conservative variance estimator by ignoring the projection term and the non-identifiable piece D^F.

Appendix B: The TMLE is an asymptotically linear estimator of the SATE in a pair-matched trial

First, we review the asymptotic linearity results of Balzer et al. (2015) for estimation and inference of the the statistical parameter corresponding to the conditional average treatment effect (CATE) (Abadie and Imbens, 2002) in a trial with adaptive pair-matching:

$$\begin{aligned}\Psi^{\mathcal{C}}(P_0) &= \frac{1}{n}\sum_{i=1}^{n}\left[E_0(Y_i|A_i = 1, W_i) - E_0(Y_i|A_i = 0, W_i)\right] \\ &= \frac{1}{n}\sum_{i=1}^{n}\left[\bar{Q}_0(1, W_i) - \bar{Q}_0(0, W_i)\right].\end{aligned}$$

Then, we provide a theorem showing that the TMLE for the SATE is asymptotically normal in a trial with adaptive pair-matching, which results in $n/2$ conditionally independent copies of $\bar{O}_j = \big(O_{j1}, O_{j2}\big) = \big((W_{j1}, A_{j1}, Y_{j1}), (W_{j2}, A_{j2}, Y_{j2})\big)$.

The TMLE for conditional estimand $\Psi^{\mathcal{C}}(P_0)$ is defined by the following substitution estimator:

$$\Psi_n(P_n) = \frac{1}{n}\sum_{i=1}^{n}\left[\bar{Q}_n^*(1, W_i) - \bar{Q}_n^*(0, W_i)\right]$$

where $\bar{Q}_n^*(A, W)$ denotes the targeted estimator. Under the following assumptions, the TMLE for $\Psi^{\mathcal{C}}(P_0)$ is asymptotically linear:

$$\Psi_n(P_n) - \Psi^{\mathcal{C}}(P_0) = \frac{1}{n/2}\sum_{j=1}^{n/2}\bar{D}^C(\bar{Q}, \bar{Q}_0, g_0)(\bar{O}_j) + o_P(1/\sqrt{n/2})$$

with influence curve

$$\bar{D}^C(\bar{Q}, \bar{Q}_0, g_0)(\bar{O}_j) = \frac{1}{2}\left[D^C(\bar{Q}, \bar{Q}_0, g_0)(O_{j1}) + D^C(\bar{Q}, \bar{Q}_0, g_0)(O_{j2})\right]$$

$$\text{with} \quad D^C(\bar{Q}, \bar{Q}_0, g_0)(O_i) = \left(\frac{\mathbb{I}(A_i = 1)}{g_0(A_i)} - \frac{\mathbb{I}(A_i = 0)}{g_0(A_i)}\right)\big(Y_i - \bar{Q}(A_i, W_i)\big) - \big[\bar{Q}_0 W_i) - \bar{Q}(W_i)\big]$$

where $\bar{Q}(A, W)$ denotes the limit of the targeted estimator of the conditional mean function $\bar{Q}_0(A, W)$; the marginal probability of being assigned the treatment or the control is known: $g_0(A) = P_0(A) = 0.5$, and $\bar{Q}(W) = \bar{Q}(1, W) - \bar{Q}(0, W)$ denotes the difference in the treatment-specific conditional means (Balzer et al., 2015). We assume

- Uniform bound: Assume $\sup_{\bar{Q}\in\mathcal{F}} \sup_O \mid \left(\frac{\mathbb{I}(A_i=1)}{g_0(A_i)} - \frac{\mathbb{I}(A_i=0)}{g_0(A_i)}\right)\left(Y_i - \bar{Q}(A_i, W_i)\right) \mid < M < \infty$ where $\mathcal{F}$ is the set of multivariate real valued functions so that $\bar{Q}_n^*$ is an element of $\mathcal{F}$ with probability 1 and where the second supremum is over a set that contains the support of each O_i.

- Convergence of variances: Assume that for a specified $\{\sigma^{2,\mathcal{C}}(\bar{Q}) : \bar{Q} \in \mathcal{F}\}$, for any $\bar{Q} \in \mathcal{F}$, $\frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n \bar{D}^C(\bar{Q}, \bar{Q}_0, g_0)^2 \to \sigma^{2,\mathcal{C}}(\bar{Q})$ a.s (i.e., for almost every $(W^n, n \geq 1)$). Throughout $P_0^n f = E_0[f|W^n]$ denotes the conditional expectation of a function f of $O^n = (O_1, \ldots, O_n)$, given the vector of baseline covariates $W^n = (W_1, \ldots, W_n)$.

- Convergence of $\bar{Q}_n^*$ to some limit: For any $\bar{Q}_1, \bar{Q}_2 \in \mathcal{F}$, we define $\sigma_n^2(\bar{Q}_1 - \bar{Q}_2) = \frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n\{\bar{D}^C(\bar{Q}_1, \bar{Q}_0, g_0) - \bar{D}^C(\bar{Q}_2, \bar{Q}_0, g_0)\}^2$. Assume that for a particular $\bar{Q} \in \mathcal{F}$, $\sigma_n^2(\bar{Q}_n^* - \bar{Q}) \to 0$ in probability as $n \to \infty$.

- Entropy condition: Let $\mathcal{F}^d = \{f_1 - f_2 : f_1, f_2 \in \mathcal{F}\}$. Let $N(\epsilon, \sigma_n, \mathcal{F}^d)$ be the covering number of the class $\mathcal{F}^d$ w.r.t norm/dissimilarity $\parallel f \parallel = \sigma_n(f)$. Assume that the class $\mathcal{F}$ satisfies $\lim_{\delta_n \to 0} \int_0^{\delta_n} \sqrt{\log N(\epsilon, \sigma_n, \mathcal{F}^d)} d\epsilon = 0$.

Theorem 3. *Let W denote the measured baseline covariates; A denote the intervention assignment and Y denote the outcome. A randomized trial with adaptive pair-matching results in $n/2$ conditionally independent copies of paired random variable*

$$\bar{O}_j = \left(O_{j1}, O_{j2}\right) = \left((W_{j1}, A_{j1}, Y_{j1}), (W_{j2}, A_{j2}, Y_{j2})\right)$$

where index $j = \{1, \ldots, n/2\}$ denotes the partitioning of the study units $\{1, \ldots n\}$ into matched pairs according to similarity on their baseline covariates $W^n = (W_1, \ldots, W_n)$. Our target of inference is the sample average treatment effect (SATE) (Neyman, 1923):

$$\Psi^{\mathcal{S}}(P_{U,O}) = \frac{1}{n}\sum_{i=1}^{n} Y_i(1) - Y_i(0)$$

where $P_{U,O}$ denotes the joint distribution of the background factors $U = (U_W, U_A, U_Y)$ and observed factors $O = (W, A, Y)$. Under the above conditions, the TMLE $\Psi_n(P_n) = \frac{1}{n}\sum_{i=1}^{n} \bar{Q}_n^*(1, W_i) - \bar{Q}_n^*(0, W_i)$ is an asymptotically linear estimator of the SATE:

$$\Psi_n(P_n) - \Psi^{\mathcal{S}}(P_{U,O}) = \frac{1}{n/2}\sum_{j=1}^{n/2} \bar{D}^{\mathcal{S}}(\bar{Q}, \bar{Q}_0, g_0)(\bar{U}_j, \bar{O}_j) + o_P(1/\sqrt{n/2})$$

with influence curve

$$\bar{D}^{\mathcal{S}}(\bar{Q}, \bar{Q}_0, g_0)(\bar{U}_j, \bar{O}_j) = \bar{D}^C(\bar{Q}, \bar{Q}_0, g_0)(\bar{O}_j) - \bar{D}^F(\bar{Q}_0)(\bar{U}_j, \bar{O}_j)$$

where $\bar{Q}(A, W)$ denotes the limit of the targeted estimator of the conditional mean function $\bar{Q}_0(A, W)$ and where the marginal probability of being assigned the treatment or the control is known $g_0(A) = P_0(A)$, and where the pair's unobserved factors are denoted $\bar{U}_j = \left(U_{j1}, U_{j2}\right)$.

The first component $\bar{D}^C(\bar{Q}, \bar{Q}_0, g_0)(\bar{O}_j)$ is the influence curve for the TMLE targeting the conditional estimand $\Psi^{\mathcal{C}}(P_0) = \frac{1}{n}\sum_{i=1}^{n}\left[\bar{Q}_0(1, W_i) - \bar{Q}_0(0, W_i)\right]$ in a trial with adaptive pair-matching:

$$\bar{D}^C(\bar{Q}, \bar{Q}_0, g_0)(\bar{O}_j) = \frac{1}{2}\left[D^C(\bar{Q}, \bar{Q}_0, g_0)(O_{j1}) + D^C(\bar{Q}, \bar{Q}_0, g_0)(O_{j2})\right]$$

$$\text{with } D^C(\bar{Q}, \bar{Q}_0, g_0)(O_i) = \left(\frac{\mathbb{I}(A_i = 1)}{g_0(A_i)} - \frac{\mathbb{I}(A_i = 0)}{g_0(A_i)}\right)\left(Y_i - \bar{Q}(A_i, W_i)\right) - \left[\bar{Q}_0(W_i) - \bar{Q}(W_i)\right]$$

The second component $\bar{D}^F(\bar{Q}_0)(\bar{U}_j, \bar{O}_j)$ is the following function of the paired unobserved data $\bar{U}_j = (U_{j1}, U_{j2})$ and observed data $\bar{O}_j = (O_{j1}, O_{j2})$:

$$\bar{D}^F(\bar{Q}_0)(\bar{U}_j, \bar{O}_j) = \frac{1}{2}\Big[D^F(\bar{Q}_0)(U_{j1}, O_{j1}) + D^F(\bar{Q}_0)(U_{j2}, O_{j2})\Big]$$
$$\text{with } D^F(\bar{Q}_0)(U_i, O_i) = Y_i(1) - Y_i(0) - \bar{Q}_0(W_i).$$

In a pair-matched trial, the standardized TMLE for the SATE is asymptotically normal with mean 0 and variance $\sigma^{2,\mathcal{S}}$ given by the limit of

$$\sigma_n^{2,\mathcal{S}} = \frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n\Big\{\bar{D}^{\mathcal{S}}(\bar{Q}, \bar{Q}_0, g_0)(\bar{U}_j, \bar{O}_j)\Big\}^2$$

where $P_0^n f = E_0[f|W^n]$ denotes the conditional expectation, given the vector of baseline covariates $W^n = (W_1, \ldots, W_n)$.

Proof. Let $\bar{Q}_0(W) = \bar{Q}_0(1, W) - \bar{Q}_0(0, W)$ denote the true difference in treatment-specific means. We can write the deviation between the TMLE $\Psi_n(P_n)$ for the conditional estimand $\Psi^{\mathcal{C}}(P_0)$ and the SATE as

$$\begin{aligned}
&\Psi_n(P_n) - \Psi^{\mathcal{S}}(P_{U,O}) \\
&\quad = \Psi_n(P_n) - \Psi^{\mathcal{C}}(P_0) - \big[\Psi^{\mathcal{S}}(P_{U,O}) - \Psi^{\mathcal{C}}(P_0)\big] \\
&\quad = \frac{1}{n/2}\sum_{j=1}^{n/2} \bar{D}^C(\bar{O}_j) - \big[\Psi^{\mathcal{S}}(P_{U,O}) - \Psi^{\mathcal{C}}(P_0)\big] + o_P(1/\sqrt{n/2}) \\
&\quad = \frac{1}{n/2}\sum_{j=1}^{n/2} \bar{D}^C(\bar{O}_j) - \left[\frac{1}{n}\sum_{i=1}^{n} Y_i(1) - Y_i(0) - \bar{Q}_0(W_i)\right] + o_P(1/\sqrt{n/2}) \\
&\quad = \frac{1}{n/2}\sum_{j=1}^{n/2} \left[\bar{D}^C(\bar{O}_j) - \frac{1}{2}\Big(Y_{j1}(1) - Y_{j1}(0) - \bar{Q}_0(W_{j1}) + Y_{j2}(1) - Y_{j2}(0) - \bar{Q}_0(W_{j2})\Big)\right] + o_P(1/\sqrt{n/2}) \\
&\quad = \frac{1}{n/2}\sum_{j=1}^{n/2} \Big[\bar{D}^C(\bar{O}_j) - \bar{D}^F(\bar{U}_j, \bar{O}_j)\Big] + o_P(1/\sqrt{n/2})
\end{aligned}$$

where $\bar{D}^C(\bar{O}_j)$ is the influence curve of the TMLE for the conditional estimand $\Psi^{\mathcal{C}}(P_0)$ under adaptive pair-matching and where $\bar{D}^F(\bar{U}_j, \bar{O}_j)$ is the following function:

$$\bar{D}^F(\bar{U}_j, \bar{O}_j) = \frac{1}{2}\Big[D^F(U_{j1}, O_{j1}) + D^F(U_{j2}, O_{j2})\Big]$$
$$\text{with } D^F(U_i, O_i) = Y_i(1) - Y_i(0) - \big[\bar{Q}_0(1, W_i) - \bar{Q}_0(0, W_i)\big].$$

Thus, we have shown the TMLE is an asymptotically linear estimator of the SATE in a trial with adaptive pair-matching:

$$\Psi_n(P_n) - \Psi^{\mathcal{S}}(P_{U,O}) = \frac{1}{n/2}\sum_{j=1}^{n/2} \bar{D}^{\mathcal{S}}(\bar{U}_j, \bar{O}_j) + o_P(1/\sqrt{n/2})$$

with influence curve

$$\bar{D}^{\mathcal{S}}(\bar{U}_j, \bar{O}_j) = \bar{D}^C(\bar{O}_j) - \bar{D}^F(\bar{U}_j, \bar{O}_j).$$

□

Strictly speaking, the influence curve must only be a function of the observed data. Nonetheless, the theorem is sufficient to prove asymptotic normality and consistency of the TMLE.

Appendix B.1: Variance and variance estimation for the TMLE of the SATE in a pair-matched trial

Theorem 4. *The standardized TMLE for the SATE is asymptotically normal with mean 0 and variance given by the limit of*

$$\sigma_n^{2,\mathcal{S}} = \frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n\Big\{\bar{D}^{\mathcal{S}}(\bar{Q},\bar{Q}_0,g_0)(\bar{U}_j,\bar{O}_j)\Big\}^2$$
$$= \frac{1}{n/2}\sum_{j=1}^{n/2}\Big[P_0^n\Big\{\bar{D}^C(\bar{Q},\bar{Q}_0,g_0)(\bar{O}_j)\Big\}^2 - P_0^n\Big\{\bar{D}^F(\bar{Q}_0)(\bar{U}_j,\bar{O}_j)\Big\}^2\Big].$$

Proof. The conditional variance can be expressed as

$$\sigma_n^{2,\mathcal{S}} = \frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n\Big\{\bar{D}^{\mathcal{S}}(\bar{U}_j,\bar{O}_j)\Big\}^2$$
$$= \frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n\Big\{\bar{D}^C(\bar{O}_j) - \bar{D}^F(\bar{U}_j,\bar{O}_j)\Big\}^2$$
$$= \frac{1}{n/2}\sum_{j=1}^{n/2}\Big[P_0^n\Big\{\bar{D}^C(\bar{O}_j)\Big\}^2 + P_0^n\Big\{\bar{D}^F(\bar{U}_j,\bar{O}_j)\Big\}^2 - 2P_0^n\Big\{\bar{D}^C(\bar{O}_j)\times\bar{D}^F(\bar{U}_j,\bar{O}_j)\Big\}\Big].$$

The conditional covariance of the $\bar{D}^C(\bar{O}_j)$ and $\bar{D}^F(\bar{U}_j,\bar{O}_j)$ components is

$$P_0^n\Big\{\bar{D}^C(\bar{O}_j)\times\bar{D}^F(\bar{U}_j,\bar{O}_j)\Big\} = \frac{1}{4}P_0^n\Big\{\big[D^C(O_{j1})+D^C(O_{j2})\big]\times\big[D^F(U_{j1},O_{j1})+D^F(U_{j2},O_{j2})\big]\Big\}$$
$$= \frac{1}{4}\Big[P_0^n\{D^C(O_{j1})\times D^F(U_{j1},O_{j1})\} + P_0^n\{D^C(O_{j1})\times D^F(U_{j2},O_{j2})\}$$
$$+ P_0^n\{D^C(O_{j2})\times D^F(U_{j1},O_{j1})\} + P_0^n\{D^C(O_{j2})\times D^F(U_{j2},O_{j2})\}\Big].$$

As shown in Appendix A.1, the covariance of the $D^C(O_i)$ and $D^F(O_i)$ components is equal to the variance of $D^F(O_i)$. Therefore, we have

$$P_0^n\Big\{D^C(O_{j1})\times D^F(U_{j1},O_{j1})\Big\} = P_0^n\Big\{D^F(U_{j1},O_{j2})\Big\}^2$$
$$P_0^n\Big\{D^C(O_{j2})\times D^F(U_{j2},O_{j2})\Big\} = P_0^n\Big\{D^F(U_{j2},O_{j2})\Big\}^2.$$

The conditional covariance term of $D^C(O_{j1})$ and $D^F(U_{j2},O_{j2})$ is given by

$$P_0^n[D^C(O_{j1})\times D^F(U_{j2},O_{j2})]$$
$$= P_0^n\Big[\Big\{\Big(\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})} - \frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\Big)\big(Y_{j1}-\bar{Q}(A_{j1},W_{j1})\big) - \big(\bar{Q}_0(W_{j1})-\bar{Q}(W_{j1})\big)\Big\}\times D^F(U_{j2},O_{j2})\Big]$$
$$= P_0^n\Big[\Big(\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})} - \frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\Big)\big(Y_{j1}-\bar{Q}(A_{j1},W_{j1})\big)\times D^F(U_{j2},O_{j2})\Big]$$
$$- P_0^n\Big[\big(\bar{Q}_0(W_{j1})-\bar{Q}(W_{j1})\big)\times D^F(U_{j2},O_{j2})\Big].$$

For the first term, we have

$$
\begin{aligned}
&P_0^n\Bigg[\left(\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})}-\frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\right)\big(Y_{j1}-\bar{Q}(A_{j1},W_{j1})\big)\times D^F(U_{j2},O_{j2})\Bigg]\\
&=P_0^n\Bigg[\left(\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})}-\frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\right)\big(Y_{j1}-\bar{Q}(A_{j1},W_{j1})+\bar{Q}_0(A_{j1},W_{j1})-\bar{Q}_0(A_{j1},W_{j1})\big)\times D^F(U_{j2},O_{j2})\Bigg]\\
&=P_0^n\Bigg[\left(\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})}-\frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\right)\big(Y_{j1}-\bar{Q}_0(A_{j1},W_{j1})\big)\times D^F(U_{j2},O_{j2})\Bigg]\\
&+P_0^n\Bigg[\left(\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})}-\frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\right)\big(\bar{Q}_0(A_{j1},W_{j1})-\bar{Q}(A_{j1},W_{j1})\big)\times D^F(U_{j2},O_{j2})\Bigg]
\end{aligned}
$$

It follow that this equals:

$$
\begin{aligned}
&P_0^n\left[\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})}\big(Y_{j1}(1)-\bar{Q}_0(1,W_{j1})\big)\times D^F(U_{j2},O_{j2})\right]\\
&-P_0^n\left[\frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\big(Y_{j1}(0)-\bar{Q}_0(0,W_{j1})\big)\times D^F(U_{j2},O_{j2})\right]\\
&+P_0^n\left[\frac{\mathbb{I}(A_{j1}=1)}{g_0(1|W_{j1})}\big(\bar{Q}_0(1,W_{j1})-\bar{Q}(1,W_{j1})\big)\times D^F(U_{j2},O_{j2})\right]\\
&-P_0^n\left[\frac{\mathbb{I}(A_{j1}=0)}{g_0(0|W_{j1})}\big(\bar{Q}_0(0,W_{j1})-\bar{Q}(0,W_{j1})\big)\times D^F(U_{j2},O_{j2})\right]
\end{aligned}
$$

Under the randomization assumption, we have

$$
E_0\left[\frac{\mathbb{I}(A_{j1}=a)}{g_0(a|W_{j1})}\middle|Y_{j1}(1),Y_{j1}(0),W_{j1},Y_{j2}(1),Y_{j2}(0),W_{j2}\right]=1
$$

Therefore, the sum of first two terms reduce to the covariance of the D^F components within a matched pair:

$$
P_0^n\Big[\big[Y_{j1}(1)-Y_{j1}(0)-\bar{Q}_0(W_{j1})\big]\times\big[Y_{j2}(1)-Y_{j2}(0)-\bar{Q}_0(W_{j2})\big]\Big]=P_0^n\Big[D^F(U_{j1},O_{j1})\times D^F(U_{j2},O_{j2})\Big],
$$

and the sum of the last two terms is

$$
P_0^n\Big[\big(\bar{Q}_0(W_{j1})-\bar{Q}(W_{j1})\big)\times D^F(U_{j2},O_{j2})\Big].
$$

We have that the conditional covariance of $D^C(O_{j1})$ and $D^F(U_{j2},O_{j2})$ equals the covariance of the D^F components within a matched pair:

$$
P_0^n\big[D^C(O_{j1})\times D^F(U_{j2},O_{j2})\big]=P_0^n\big[D^F(U_{j1},O_{j1})\times D^F(U_{j2},O_{j2})\big].
$$

Under the same reasoning, the conditional covariance term of $D^C(O_{j2})$ and $D^F(U_{j1},O_{j2})$ equals the covariance of the D^F components within a matched pair

$$
P_0^n\big[D^C(O_{j2})\times D^F(U_{j1},O_{j1})\big]=P_0^n\big[D^F(U_{j1},O_{j1})\times D^F(U_{j2},O_{j2})\big]
$$

Therefore, the conditional covariance of the $\bar{D}^C(\bar{O}_j)$ and $\bar{D}^F(\bar{U}_j, \bar{O}_j)$ components equals the conditional variance of the pairwise $\bar{D}^F(\bar{U}_j, \bar{O}_j)$ component

$$
\begin{aligned}
P_0^n\Big\{\bar{D}^C(\bar{O}_j) \times \bar{D}^F(\bar{U}_j, \bar{O}_j)\Big\} &= \frac{1}{4}P_0^n\Big\{D^F(U_{j1}, O_{j1})\Big\}^2 + \frac{1}{4}P_0^n\Big\{D^F(U_{j2}, O_{j2})\Big\}^2 \\
&\quad + \frac{1}{2}P_0^n\Big\{D^F(U_{j1}, O_{j1}) \times D^F(U_{j2}, O_{j2})\Big\} \\
&= P_0^n\Big\{\frac{1}{2}\big(D^F(U_{j1}, O_{j1}) + D^F(U_{j2}, O_{j2})\big)\Big\}^2 \\
&= P_0^n\Big\{\bar{D}^F(\bar{U}_j, \bar{O}_j)\Big\}^2
\end{aligned}
$$

Thus, the asymptotic variance of the standardized estimator the SATE in a trial with pair-matching is given by the limit of

$$
\sigma_n^{2,\mathcal{S}} = \frac{1}{n/2}\sum_{j=1}^{n/2}\left[P_0^n\Big\{\bar{D}^C(\bar{O}_j)\Big\}^2 - P_0^n\Big\{\bar{D}^F(\bar{U}_j, \bar{O}_j)\Big\}^2\right]
$$

□

The asymptotic variance of the standardized TMLE for the SATE $\sigma^{2,\mathcal{S}}$ is always less than or equal to the asymptotic variance of the TMLE for the conditional parameter $\sigma^{2,\mathcal{C}}$ in a pair-matched trial. As shown in Balzer et al. (2015), we can estimate the upper bound as

$$
\hat{\sigma}^{2,\mathcal{S}} = \hat{\sigma}^{2,\mathcal{C}} = \frac{1}{n/2}\sum_{j=1}^{n/2}\Big\{\hat{\bar{D}}^{\mathcal{C}}(\bar{Q}_n^*, g_0)(\bar{O}_j)\Big\}^2
$$

$$
\text{where} \quad \hat{\bar{D}}^{\mathcal{C}}(\bar{Q}_n^*, g_0)(\bar{O}_j) = \frac{1}{2}\Big[\hat{D}^{\mathcal{C}}(\bar{Q}_n^*, g_0)(O_{j1}) + \hat{D}^{\mathcal{C}}(\bar{Q}_n^*, g_0)(O_{j2})\Big]
$$

$$
\text{and} \quad \hat{D}^{\mathcal{C}}(\bar{Q}_n^*, g_0)(O_i) = \left(\frac{\mathbb{I}(A_i = 1)}{g_0(A_i)} - \frac{\mathbb{I}(A_i = 0)}{g_0(A_i)}\right)\big(Y_i - \bar{Q}_n^*(A_i, W_i)\big).
$$

Ordering the observations within matched pairs, such that the first corresponds to the unit randomized to the intervention ($A_{j1} = 1$) and the second to the control ($A_{j2} = 0$), it follows that

$$
\hat{\bar{D}}^{\mathcal{C}}(\bar{Q}_n^*, g_0)(\bar{O}_j) = \big(Y_{j1} - \bar{Q}_n^*(1, W_{j1})\big) - \big(Y_{j2} - \bar{Q}_n^*(0, W_{j2})\big)
$$

allowing us to represent the variance estimator as the sample variance of the difference in residuals within matched pairs:

$$
\hat{\sigma}^{2,\mathcal{S}} = \hat{\sigma}^{2,\mathcal{C}} = \frac{1}{n/2}\sum_{j=1}^{n/2}\Big\{\big(Y_{j1} - \bar{Q}_n^*(1, W_{j1})\big) - \big(Y_{j2} - \bar{Q}_n^*(0, W_{j2})\big)\Big\}^2.
$$

This variance estimator will be consistent if there is no heterogeneity in the treatment effect within strata of covariates (i.e. if the variance of the $D^{\mathcal{F}}$ component is zero) *and* if the conditional mean function $\bar{Q}_0(A, W)$ is consistently estimated. Otherwise, the variance estimator will be conservative.

Appendix C: Comparison of the asymptotic variance of the TMLEs for the SATE with and without pair-matching

Let $P_0^n f$ to denote the conditional expectation of a function f of O^n given W^n. As presented in Balzer et al. (2015), the asymptotic variances of the standardized TMLEs for the conditional parameter $\Psi^{\mathcal{C}}(P_0)$ in a trial without pair-matching and a trial with pair-matching are given by the limits of

$$\begin{aligned}\sigma^{2,\mathcal{C}}_{n,non-matched} &= \frac{1}{n}\sum_{i=1}^{n} P_0^n\left\{D^C(O_i)\right\}^2 \\ &= \frac{1}{n}\sum_{i=1}^{n}\left\{2E_0\left[\left(Y_i-\bar{Q}(1,W_i)\right)^2\middle| A_i=1,W^n\right]+2E_0\left[\left(Y_i-\bar{Q}(0,W_i)\right)^2\middle| A_i=0,W^n\right]\right. \\ &\quad\left. +\left[\bar{Q}_0(1,W_i)-\bar{Q}(1,W_i)+\bar{Q}_0(0,W_i)-\bar{Q}(0,W_i)\right]^2\right\}\end{aligned}$$

and

$$\sigma^{2,\mathcal{C}}_{n,matched} = \frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n\left\{\bar{D}^C(\bar{O}_j)\right\}^2 = 0.5\sigma^{2,\mathcal{C}}_{n,non-matched}-\rho_0,$$

respectively. ρ_0 is the limit of the following pairwise product:

$$\begin{aligned}\rho_0 = \frac{1}{n}\sum_{j=1}^{n/2}\Big\{&\left[\bar{Q}_0(1,W_{j1})-\bar{Q}(1,W_{j1})+\bar{Q}_0(0,W_{j1})-\bar{Q}(0,W_{j1})\right] \\ &\times\left[\bar{Q}_0(1,W_{j2})-\bar{Q}(1,W_{j2})+\bar{Q}_0(0,W_{j2})-\bar{Q}(0,W_{j2})\right]\Big\}.\end{aligned}$$

Also recall that in the pair-matched design, we have

$$\begin{aligned}\frac{1}{n/2}\sum_{j=1}^{n/2} P_0^n\left\{\bar{D}^F(\bar{U}_j,\bar{O}_j)\right\}^2 = \frac{1}{n/2}\sum_{j=1}^{n/2}\Big[&\frac{1}{4}P_0^n\left\{D^F(U_{j1},O_{j1})\right\}^2+\frac{1}{4}P_0^n\left\{D^F(U_{j2},O_{j2})\right\}^2 \\ &+\frac{1}{2}P_0^n\left\{D^F(U_{j1},O_{j1})\times D^F(U_{j2},O_{j2})\right\}\Big].\end{aligned}$$

Substituting these into the formulas for the asymptotic variances of the standardized estimators for the sample effect, we have

$$\begin{aligned}\sigma^{2,\mathcal{S}}_{n,non-matched} &= \frac{1}{n}\sum_{i=1}^{n}\left[P_0^n\left\{D^C(O_i)\right\}^2 - P_0^n\left\{D^F(U_i,O_i)\right\}^2\right] \\ &= \sigma^{2,\mathcal{C}}_{n,non-matched}-\frac{1}{n}\sum_{i=1}^{n}P_0^n\left\{\left(Y_i(1)-Y_i(0)-\bar{Q}_0(W_i)\right)^2\right\}.\end{aligned}$$

and

$$\begin{aligned}\sigma^{2,\mathcal{S}}_{n,matched} &= \frac{1}{n/2}\sum_{j=1}^{n/2}P_0^n\left\{\bar{D}^C(\bar{O}_j)\right\}^2 - \frac{1}{n/2}\sum_{j=1}^{n/2}P_0^n\left\{\bar{D}^F(\bar{U}_j,\bar{O}_j)\right\}^2 \\ &= 0.5\sigma^{2,\mathcal{C}}_{n,non-matched}-\rho_0-\frac{1}{2n}\sum_{i=1}^{n}P_0^n\left\{\left(Y_i(1)-Y_i(0)-\bar{Q}_0(W_i)\right)^2\right\} \\ &\quad -\frac{1}{n}\sum_{j=1}^{n/2}P_0^n\left\{D^F(U_{j1},O_{j1})\times D^F(U_{j2},O_{j2})\right\} \\ &= 0.5\sigma^{2,\mathcal{S}}_{n,non-matched}-\rho_0-\phi_0\end{aligned}$$

where

$$\phi_0 = \frac{1}{n}\sum_{j=1}^{n/2} P_0^n\{D^F(U_{j1},O_{j1}) \times D^F(U_{j2},O_{j2})\}$$
$$= \frac{1}{n}\sum_{j=1}^{n/2} P_0^n\Big\{\big(Y_{j1}(1) - Y_{j1}(0) - \bar{Q}_0(W_{j1})\big) \times \big(Y_{j2}(1) - Y_{j2}(0) - \bar{Q}_0(W_{j2})\big)\Big\}.$$

Thus, the asymptotic variances of the TMLE for the SATE in a non-matched trial is given by the limit of $\sigma^{2,\mathcal{S}}_{n,non-matched}/n$ whereas the asymptotic variance of the TMLE in a pair-matched trial is given by the limit of $\sigma^{2,\mathcal{S}}_{n,matched}/(n/2) = \sigma^{2,\mathcal{S}}_{n,non-matched}/n - 2\rho_0/n - 2\phi_0/n$. As discussed in Balzer et al. (2015), when we match well on measured and unmeasured factors, the deviations between the true conditional means $\bar{Q}_0(A,W)$ and the limit of the estimated $\bar{Q}(A,W)$ is expected to be positively correlated within matched pairs:

$$\rho_0 \geq 0.$$

Furthermore, when we match on predictive factors, the deviations between the unit-specific treatment effect and the treatment effect within covariate strata is expected to be positively correlated within matched pairs:

$$\phi_0 \geq 0.$$

Therefore, in most practical settings, the pair-matched trial will be more efficient than its non-matched counterpart for estimation and inference of the sample effect. Even under consistent estimation of the conditional mean outcome $\bar{Q}_0(A,W)$ (and therefore $\rho_0 = 0$), there is still will be a gain for matching if $\phi_0 > 0$.

Appendix D: `R` Code

Full `R` code for the simulations and estimators is available below and at `http://works.bepress.com/laura_balzer/26/`. Please see the website for updates. We also note that the following code applies to binary or bounded continuous outcomes.

```
#################
# Sample R code and Simulations to illustrate estimation and inference
# for the sample average treatment effect in trials with and without pair-matching.
# Demonstrates the unadjusted estimator,
# TMLE with logistic regression for outcome regression E_0(Y|A,W)=Qbar_0(A,W),
# and TMLE with SuperLearner for Qbar_0(A,W)
#
# Programmer: Laura Balzer (lbbalzer@hsph.harvard.edu)
# Please email with questions, concerns or requests
#
# R version 3.2.1
#
# Last update: Dec 8, 2015
####################

#-------------------------------
# simulate.data.and.run: function to generate the simulated data
# and run the estimators
```

```
#-------------------------------
simulate.data.and.run<- function(){

  # directly simulate the full data (covariates and counterfactual outcomes)
  X.full<- generateData(n)

  # Sample average counterfactual outcome under A=a
  R1<- mean(X.full$Y.1)
  R0<- mean(X.full$Y.0)

  # SATE is the sample average difference in the counterfactuals
  SATE= R1-R0

  if(PAIRED){
    # if pair-matching trial, match units and randomize the treatment
    X.all <- doPairMatching(matchData=X.full[, matchOn], fullData=X.full)

  } else{
    # Otherwise, assign the treatment - guarantee that n/2 are treated
    A<- rbinom(n/2, 1, 0.5)
    A.2<- ifelse(A==1, 0, 1)
    A <- sample( c(A,A.2))
    X.all <- cbind( X.full, paired=rep(NA, n), A)
  }

  # we observe the counterfactual outcome corresponding to the observed exp
  Y<- ifelse(X.all$A, X.all$Y.1, X.all$Y.0)
  X.all<- cbind(X.all, Y)

  #-----------------
  # Estimation and inference
  #-----------------

  unadj<- doTMLE(SATE, data=X.all, Qadj='U', family='binomial')

  adj.AW1<- doTMLE(SATE, data=X.all, Qadj='W.1', Qform=as.formula(Y~A*W.1), family='binomial')

  Qadj<- c('W.1','W.2', 'W.3', 'W.4', 'W.5')

  adj.SL<- doTMLE(SATE, data=X.all, Qadj=Qadj, family='binomial', Do.SL=T)

  RETURN<- list(unadj=unlist(unadj),  adj.AW1=unlist(adj.AW1),
    adj.SL =unlist(adj.SL) )

  RETURN
}

#--------------------------
# generateData: function to generate the full data
# including baseline covariates and the counterfactual outcomes
```

```
#--------------------------
generateData<- function(n){

  U.Y<- generateU.Y(n)
  W<- generateW(n)
  Y.0<- generateY(W=W, A=0, U.Y=U.Y)
  if(EFFECT){
    Y.1<- generateY(W=W, A=1, U.Y=U.Y)
  } else{
    Y.1 <- Y.0
  }
  data.frame(W, Y.0,Y.1)
}

#------------------
# additional functions to generate the simulated data
#-------------------

# generate unmeasured U.Y
generateU.Y<- function(n){
  rnorm(n, 0, SD)
}

# generate the baseline covariates W
generateW<- function(n) {

  Sigma<- matrix(CORR.W*SD*SD, nrow=3, ncol=3)
  diag(Sigma)<- SD^2

  W<- cbind(rnorm(n,0,1), rnorm(n,0,1), mvrnorm(n, rep(0,3), Sigma))

  data.frame(U=1, W=W )
}

# generate the outcome Y
generateY<- function(W, A, U.Y) {
  .2*plogis(1*A + .75*W$W.1 + .75*W$W.2 + 1.25*W$W.3 + U.Y + .75*W$W.1*A - .5*W$W.2*A - A*U.Y )
}


#----------------------
# get.PATE: function to calculate the true value of the PATE
# over a population of 500,000 units
#----------------------

get.PATE<- function(pop= 500000){

  X.full<- generateData(pop)

  # average counterfactual outcome under A=a for the population
```

```
  R1<- mean( X.full$Y.1)
  R0<- mean( X.full$Y.0)

  RD= R1-R0

  c(R1, R0, RD)
}

#--------------------
# doPairMatching - function to pair-match units (fullData)
# based on the matching covariates (matchData)
# and assign the treatment within the resulting matched pairs
# Requires nbpMatching package
#-----------------------

doPairMatching<- function(matchData, fullData){

  dist<- distancematrix(gendistance(data.frame(matchData)))
  matches<- nonbimatch(dist)

  # matches contains ids for the pair as well as the distance measure
  grpA<- as.numeric(matches$halves[,'Group1.Row'])
  grpB<- as.numeric(matches$halves[,'Group2.Row'])

  npairs<- length(grpA)
  X1<- data.frame(fullData[grpA, ], pair=1:npairs, A= rbinom(npairs, 1, .5))
  X2<- data.frame(fullData[grpB, ], pair=1:npairs, A= ifelse(X1$A==1, 0, 1 ))

  Xpaired<- NULL
  for(i in 1:npairs){
    Xpaired<- rbind(Xpaired, X1[i,], X2[i,])
  }
  Xpaired
}

#--------------------------------
# doTMLE: function to run full TMLE and get inference
# input: SATE (sample ATE for that study), data,
#   Qadj (candidate adjustment variables for Qbar_0(A,W))
#   Qform (the form of the outcome regression), family (binomial for logistic regression),
#   Do.SL (whether or not do SuperLearner)
# output: estimation and inference for the population and sample effect
#
# Requires the SuperLearner package
#
# For further information about coding TMLE and calling SuperLearner,
# please see http://www.ucbbiostat.com/
#------------------------------------------------

doTMLE<- function(SATE, data, Qadj, Qform=as.formula(Y~.), family='binomial', Do.SL=F){
```

```
if(!Do.SL){ # if not doing SuperLearner

  X1 = X0 = X= data[,c(Qadj, 'A','Y')]
  X1$A<-1; X0$A<- 0
  glm.out<- suppressWarnings(  glm(Qform, family=family, data=X) )

  # get predicted outcomes under obs exp, txt and control
  QbarAW<- suppressWarnings( predict(glm.out, newdata=X, type="response"))
  Qbar1W<- suppressWarnings( predict(glm.out, newdata=X1, type='response'))
  Qbar0W<- suppressWarnings( predict(glm.out, newdata=X0, type='response') )

} else{   # do super learner

  X1 = X0 = X= data[,c(Qadj, 'A')]
  X1$A<-1; X0$A<- 0
  newX<- rbind(X,X1, X0)

  # call SuperLearner
  if(PAIRED){
    # for the cross-validation step, we need to respect the unit of (conditional) independence
    Qinit<-SuperLearner(Y=data$Y, X=X, newX=newX, SL.library= QSL.LIBRARY, family="binomial",
      cvControl=list(V=n/2), id=data$pairs )
  } else{
    Qinit<-SuperLearner(Y=data$Y, X=X, newX=newX, SL.library= QSL.LIBRARY, family="binomial",
      cvControl=list(V=n/2) )
  }

  QbarAW<-Qinit$SL.predict[1:n]
  Qbar1W<-Qinit$SL.predict[(n+1): (2*n)]
  Qbar0W<-Qinit$SL.predict[(2*n+1): (3*n)]

}

# We're not estimating the known exposure mechanism,
#   but we could for greater efficiency
# For further details, email lbbalzer@hsph.harvard.edu
pscore = rep(0.5,n)

# Calculating the clever covariate
H.1W<- 1/ (pscore)
H.0W<-  -1/ (1-pscore)
H.AW<- rep(NA, n)
H.AW[data$A==1]<- H.1W[data$A==1]
H.AW[data$A==0]<- H.0W[data$A==0]

# updating step
logitUpdate<- suppressWarnings( glm(data$Y ~ -1 +offset(qlogis(QbarAW)) + H.AW,
  family="binomial"))
```

```
# estimated coefficient on the clever covariate
eps<-logitUpdate$coef

# targeted estimates of the outcome regression
QbarAW<-plogis( qlogis(QbarAW)+eps*H.AW)
Qbar0W<-plogis( qlogis(Qbar0W)+eps*H.0W)
Qbar1W<-plogis( qlogis(Qbar1W)+eps*H.1W)

# risk estimates under txt, under control and risk difference
R1<- mean(Qbar1W)
R0<- mean(Qbar0W)
RD<- mean(Qbar1W- Qbar0W)

#--------------------
# get inference via the influence curve
#--------------------

# the relevant components of the influence curve
DY<- H.AW*(data$Y- QbarAW)
DW<- Qbar1W - Qbar0W - RD

if(!PAIRED){

  var.PATE<- var(DY+DW)/n
  var.SATE<- var(DY)/n
  df=(n-2)

  est.PATE<- get.inference(truth=PATE[3], RD=RD, var=var.PATE, df=df)
  est.SATE<- get.inference(truth=SATE, RD=RD, var=var.SATE, df=df)

  RETURN<- data.frame(R1=R1, R0=R0, RD=RD, PATE=est.PATE, SATE=est.SATE)

}else{

  pairs<- data$pair
  temp<- unique(pairs)
  n.pairs<- length(temp)

  # DbarY= 1/2 sum_{i in pairs} HAW_i*(Y_i -Qbar_i)
  # Serves as the upper bound on the IC
  DY.paired<- rep(NA, n.pairs)

  for(i in 1:n.pairs){
    DY.paired[i]<- 0.5*sum(DY[ pairs== temp[i]] )
  }

  var.SATE<- var(DY.paired)/n.pairs

  df= (n.pairs -1)
  est.SATE<- get.inference(truth=SATE, RD=RD, var=var.SATE, df=df)
```

```
    # for estimation of the PATE in an Adaptive Pair-Matched Trial, see van der Laan et al. 2012
    RETURN<-  data.frame(R1=R1, R0=R0, RD=RD, SATE=est.SATE)

  }

  RETURN
}

#---------------------
# get.inference:
# input: true value of target parameter, estimate (RD), variance estimate
#   and df for t-dist
# output: variance est, test statistic, indicator of 95% CI contained the truth
#   and indicator that rejected the null at the alpha=0.05 level
#-------------------------

get.inference<- function(truth, RD, var, df){

  se<- sqrt(var)
  cutoff <- qt(0.05/2, df=df, lower.tail=F)

  cov<- (RD - cutoff*se) <= truth & truth <= (RD + cutoff*se)
  tstat <- RD/se
  reject <- abs(tstat) > cutoff

  data.frame(truth=truth, var=var, tstat=tstat, cov=cov, reject=reject)
}

#==========================================================
# The remaining are helper functions to run SuperLearner
#===========================================================

SL.glmAW1int<- function (Y, X, newX, family, obsWeights, ...) {
    fit.glm <- glm(Y ~  A + W.1 + A:W.1, data = X, family = family, weights = obsWeights)
    pred <- predict(fit.glm, newdata = newX, type = "response")
    fit <- list(object = fit.glm)
    class(fit) <- "SL.glmAW1int"
    out <- list(pred = pred, fit = fit)
    return(out)
}
SL.glmAW2int<- function (Y, X, newX, family, obsWeights, ...) {
    fit.glm <- glm(Y ~  A + W.2 + A:W.2, data = X, family = family, weights = obsWeights)
    pred <- predict(fit.glm, newdata = newX, type = "response")
    fit <- list(object = fit.glm)
    class(fit) <- "SL.glmAW2int"
    out <- list(pred = pred, fit = fit)
    return(out)
}
SL.glmAW3int<- function (Y, X, newX, family, obsWeights, ...) {
```

```
    fit.glm <- glm(Y ~  A + W.3 + A:W.3, data = X, family = family, weights = obsWeights)
    pred <- predict(fit.glm, newdata = newX, type = "response")
    fit <- list(object = fit.glm)
    class(fit) <- "SL.glmAW3int"
    out <- list(pred = pred, fit = fit)
    return(out)
}
SL.glmAW4int<- function (Y, X, newX, family, obsWeights, ...) {
    fit.glm <- glm(Y ~  A + W.4 + A:W.4, data = X, family = family, weights = obsWeights)
    pred <- predict(fit.glm, newdata = newX, type = "response")
    fit <- list(object = fit.glm)
    class(fit) <- "SL.glmAW4int"
    out <- list(pred = pred, fit = fit)
    return(out)
}
SL.glmAW5int<- function (Y, X, newX, family, obsWeights, ...) {
    fit.glm <- glm(Y ~  A + W.5 + A:W.5, data = X, family = family, weights = obsWeights)
    pred <- predict(fit.glm, newdata = newX, type = "response")
    fit <- list(object = fit.glm)
    class(fit) <- "SL.glmAW5int"
    out <- list(pred = pred, fit = fit)
    return(out)
}

#================================================================

set.seed(1)

library(MASS)
library(SuperLearner)
library(nbpMatching)

# the following are global variables - specified by the user
n<<- 30

SD<<- 1 #std deviation of baseline covariate
CORR.W<<- .65 # correlation in (W3,W4,W5)

# SuperLearner library for Qbar_0(A,W)
QSL.LIBRARY<<- c('SL.glmAW1int', 'SL.glmAW2int', 'SL.glmAW3int', 'SL.glmAW4int', 'SL.glmAW5int')

PAIRED<<- T
matchOn<<- c('W.1', 'W.4','W.5')

EFFECT<<- T

PATE<<- get.PATE()

out<- simulate.data.and.run()
```

References

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