# Chapter 19
# C-TMLE of an Additive Point Treatment Effect

Susan Gruber, Mark J. van der Laan

C-TMLE is an extension of TMLE that pursues an optimal strategy for estimation of the nuisance parameter required in the targeting step. This latter step involves maximizing an empirical criterion over a parametric working model indexed by a nuisance parameter. For the sake of introduction and demonstration, we will focus on C-TMLE of a causal effect:

$$\Psi(P_0) = E_0[E_0(Y \mid A = 1, W) - E_0(Y \mid A = 0, W)],$$

based on $n$ i.i.d. observations on the random variable $O = (W, A, Y) \sim P_0$, with nonparametric statistical model $\mathcal{M}$ for $P_0$. This target parameter depends on $P_0$ through the marginal distribution $Q_{W,0}$ of $W$ and the conditional mean $\bar{Q}_0(A, W) = E_0(Y \mid A, W)$, such that we can also write $\Psi(Q_0)$, where $Q_0 = (Q_{W,0}, \bar{Q}_0)$. We denote the treatment mechanism $P_0(A = a \mid W)$ with $g_0(a \mid W)$, $a \in \{0, 1\}$, which plays the role of the nuisance parameter in TMLE and C-TMLE. This simple target parameter and data structure is sufficiently rich to convey the essential elements of this general estimation procedure C-TMLE.

As with other double robust estimators, TMLE relies on external estimation (using, for example, log-likelihood-based super learning) of the treatment mechanism $g_0(1 \mid W) = P_0(A = 1 \mid W)$ based on the log-likelihood loss function of a candidate $g$. TMLE uses the estimator $g_n$ of $g_0$ in order to make the bias of the TMLE $\Psi(Q_n^1)$ of $\psi_0 = \Psi(Q_0)$ smaller than the bias of the initial substitution estimator $\Psi(Q_n^0)$ based on an initial estimator $Q_n^0 = (Q_{W,n}, \bar{Q}_n^0)$ of $Q_0$. Here $Q_{W,0}$ is estimated with the empirical distribution and is not updated by the TMLE. For example, if we use the squared error loss function for $\bar{Q}_0$, then we have that $\bar{Q}_n^1 = \bar{Q}_n^0 + \epsilon_n H(g_n)$, and the TMLE is defined as the substitution estimator $\Psi(Q_n^1)$, where $H(g_n)(W, A) = A/g_n(A \mid W) - (1-A)/g_n(A \mid W)$ is the clever covariate used to define the parametric fluctuation working model, and $\epsilon_n$ is the corresponding least-squares regression estimator.

The choice of estimator $g_n$ of $g_0$ can seriously affect the amount of bias reduction achieved by the TMLE $\Psi(Q_n^1)$ relative to the bias of the initial estimator $\Psi(Q_n^0)$. The

M.J. van der Laan and S. Rose, *Targeted Learning: Causal Inference for Observational and Experimental Data*, Springer Series in Statistics, DOI 10.1007/978-1-4419-9782-1_19,

likelihood for $g$ is the only available guide for estimation of $g_0$, yet not all predictors of treatment are necessarily also predictive of the outcome and thus should be included in the estimator of the treatment mechanism. In addition, a covariate that is heavily predictive of the outcome, but mildly predictive of treatment, might be a more important covariate to include in the estimator of the treatment mechanism than a covariate that is mildly predictive of the outcome and strongly predictive of the treatment, but the log-likelihood of the treatment mechanism would heavily favor the latter nonimportant covariate. As a consequence, maximum-likelihood-based estimation of $g_0$, though fully effective for estimation of $g_0$ itself, is inherently limited for the purpose of TMLE by its inability to identify true confounders of the treatment effect.

Theory advanced in van der Laan and Gruber (2010) provides the key insight that the TMLE step achieves full bias reduction as long as it uses a true conditional distribution of treatment treatment that adjusts for the covariates that are predictive of the residual bias/error $\bar{Q}_n^0(a, W) - \bar{Q}_0(a, W)$, $a \in \{0, 1\}$, of the initial estimator of the true outcome-regression $\bar{Q}_0$. This result is intuitively a natural consequence of the fact that the clever covariate can only reduce bias if it is predictive of the outcome after taking into account the initial estimator. This theoretical collaborative double-robustness result provides the motivation and theoretical underpinning of the C-TMLE described in this chapter. This chapter is adapted from Gruber and van der Laan (2010a).

The C-TMLE and TMLE are both substitution estimators of the form $\Psi(Q_n^*)$, where $Q_n^*$ is an update of $Q_n^0$. However, they differ in the subsequent targeted bias-reduction step applied to $Q_n^0$, and thereby the resulting update $Q_n^*$, and corresponding substitution estimator $\Psi(Q_n^*)$. The TMLE applies one TMLE step to $Q_n^0$ using a fully adjusted estimator $g_n$ of the treatment mechanism. On the other hand, the C-TMLE builds iteratively a sequence of candidate TMLEs $Q_{n,k}^*$ that use a $g_{n,k}$, indexed by $k = 1, \ldots, K$, for which the empirical fit of both $Q_{n,k}^*$ and $g_{n,k}$ is increasing in $k$, and it uses cross-validation *based on the loss function for* $Q_0$ to select the best TMLE among these candidates. The final estimator $g_{n,K}$ in this sequence is as nonparametric as the $g_n$ used by the TMLE and is supposed to be a consistent estimator of $g_0$. The rationale of the asymptotic consistency of C-TMLE can be phrased as follows. If, given a current running initial estimator of $\bar{Q}_0$, such as a TMLE using $g_{n,k}$, a next TMLE update of this initial estimator using an enlarged adjustment set in $g_{n,k+1}$, results in zero improvement in true fit (as meaured by cross-validation) of $\bar{Q}_0$, then the additional covariates added to the treatment mechanism cannot further reduce bias for $\psi_0$ either.

Specifically, such a sequence of candidate TMLEs and corresponding C-TMLE may be built as follows. Recall that we estimate the marginal distribution of $W$ with the empirical distribution, so that we only need to describe the C-TMLE of $\bar{Q}_0$. For simplicity, the following algorithm is presented with a set of main terms extracted from $W$. One starts with the initial estimator $\bar{Q}_n^0$. The first candidate is defined as the TMLE that fluctuates the initial estimator $\bar{Q}_n^0$, using a logistic regression model fit for the treatment mechanism that only includes the intercept. Next consider a TMLE that fluctuates $\bar{Q}_n^0$ with a logistic regression model fit of the treatment mechanism

that includes a main term (beyond the intercept). There are several such fits, each of which leads to a different TMLE. Focus on the TMLE that gives the best empirical fit to the data. If this TMLE indeed improves the $\bar{Q}_0$ empirical fit relative to the previous TMLE (in the sequence) using the intercept model for $g_0$, then this TMLE is the second candidate in the sequence of TMLEs we are building. If, on the other hand, this TMLE does not improve the empirical fit of $\bar{Q}_0$, then we do not accept this TMLE as our second candidate in the sequence of TMLEs. Instead we replace the initial estimator by the previous TMLE and we start over. We now consider a TMLE that fluctuates this new initial estimator with a logistic regression estimator of the treatment mechanism that includes the main term (beyond the intercept) that gives the best fit of the corresponding TMLE of $\bar{Q}_0$.

Since this TMLE is a fluctuation of the previous TMLE in the sequence, it will now always improve the $\bar{Q}_0$ empirical fit relative to the previous TMLE in the sequence we have built so far. Therefore, we select this TMLE as our second TMLE in the sequence. This process is iterated and results in a sequence of TMLEs $\bar{Q}^*_{n,k}$ with a corresponding estimator $g_{n,k}$ of the treatment mechanism, for which the empirical fits of both $\bar{Q}^*_{n,k}$ and $g_{n,k}$ improve in $k$. The estimator $g_{n,k}$ corresponds with a logistic regression fit with an intercept and $k-1$ main terms. Given these candidate estimators $\bar{Q}^*_{n,k}$, we select $k$ with cross-validation selector $k_n$ based on the loss function for $\bar{Q}_0$, the same loss function that was used in the TMLE step. The C-TMLE of $\bar{Q}_0$ is now defined as the corresponding $\bar{Q}^*_n = \bar{Q}^*_{n,k_n}$, and the C-TMLE of $\psi_0$ is the corresponding substitution estimator $\Psi(\bar{Q}^*_n)$. Note that this sequence of TMLEs puts in an increasing effort in targeted bias reduction (because the fit of $g_{n,k}$ is increasing in $k$), resulting in an improved empirical fit of $\bar{Q}_0$ (because the fit of $\bar{Q}^*_{n,k}$ is increasing in $k$), and cross-validation selects the largest $k$ for which the observed increase in $\bar{Q}_0$ empirical fit is still reflective of an improvement in real fit of $\bar{Q}_0$.

A common misconception is that C-TMLE might not adjust for confounders as much as the TMLE. In fact, by careful selection of covariates in the treatment mechanism, the C-TMLE typically carries out a more effective bias reduction, and thereby delivers as much or more bias reduction than TMLE, at the cost of a smaller increase in finite sample variance. In the context of sparsity, the C-TMLE may strongly outperform the TMLE. That said, in settings in which the initial estimator is poor, and a thorough understanding on what covariates to include in the treatment mechanism estimator is available, a C-TMLE that builds many candidate TMLEs to select from may perform worse than the less adaptive TMLE.

## 19.1 Linear Fluctuation and Squared Error Loss

One first needs to define a valid loss function for $\bar{Q}_0$, such as the squared error loss function $L(\bar{Q})(O) = (Y - \bar{Q}(A,W))^2$, and a fluctuation working model, so that, given an initial estimator of $\bar{Q}_0$, an estimator of the treatment mechanism $g_0$, a corresponding TMLE is well defined. Given such a definition of the TMLE, the C-TMLE algorithm can be described as follows:

*C-TMLE Algorithm*

Step 1. Construct an initial estimator $\bar{Q}_n^0$ of $\bar{Q}_0(A, W) = E_0(Y \mid A, W)$, such as the super learner based on the squared error loss function.

Step 2. Create candidate TMLEs $\bar{Q}_{n,k}^*$, using a treatment mechanism estimator $g_{n,k}$, such that the empirical fits of $\bar{Q}_{n,k}^*$ (based on the loss function for $\bar{Q}_0$) and $g_{n,k}$ are increasing in $k$. This can be carried out with a forward greedy selection algorithm, described below.

Step 3. Select the best candidate, $\bar{Q}_n^* = \bar{Q}_{n,k_n}^*$, using loss-based cross-validation using the loss function for $\bar{Q}_0$ used in the TMLE.

Step 4. Evaluate its parameter value, $\psi_n = \Psi(Q_n^*)$, based on substitution of $\bar{Q}_n^*$ and the empirical distribution $Q_{W,n}$ as estimator of the marginal distribution of $W$.

Theory requires that the sequence $(g_{n,k} : k)$ of estimators grow toward and arrive at a consistent estimator of the true $g_0$. Building nested candidate estimators $g_{n,k}$ is one particular approach that satisfies this requirement, and ensures that for all $m < k$, $g_{n,k}$ is a better empirical fit for the treatment mechanism than $g_{n,m}$. At each step $k$ in the iterative forward selection algorithm described below, it has a current initial estimator of $\bar{Q}_0$ and a current $g_{n,k}$ as a starting point. At this step $k$, it considers all the TMLE updates of the current initial estimator of $\bar{Q}_0$ using a $g_{n,k+1}$ that augments the current main term model $g_{n,k}$ with a single additional covariate $W_k$, among the remaining main terms to consider. It selects the main term that maximizes the TMLE fit of $\bar{Q}_0$. In this manner, for each $k = 1, 2, \ldots$, the $k$ step in this iterative algorithm aims to improve the fit for $g_0$ in a way that maximally increases the corresponding TMLE fit of $\bar{Q}_0$.

Let's be specific. We define a TMLE in terms of the squared error loss function and linear fluctuation model. One begins with the intercept model for $g_0$ to construct a first clever covariate, $H^*(g_{n,1})$, used to create the first targeted maximum likelihood candidate, $\bar{Q}_{n,1}^* = \bar{Q}_n^0 + \epsilon_1 H^*(g_{n,1})$, where

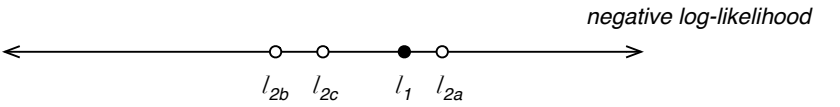
$$g_{n,1}(a \mid W) = P_n(A = a),\ a \in \{0, 1\},$$
$$H^*(g_{n,1}) = \left( \frac{I(A = 1)}{g_{n,1}(1 \mid W)} - \frac{I(A = 0)}{g_{n,1}(0 \mid W)} \right),$$

and $\epsilon_1$ is fitted by least-squares regression of $Y$ on $H^*(g_{n,1})$ with offset $\bar{Q}_n^0$. The second candidate TMLE will be based on an updated model for $g_0$ that contains the intercept and one term. The best main term is selected based on an empirical fit of the TMLE of $\bar{Q}_0$. This empirical fit is defined as the empirical sum of squared residuals at the resulting $\bar{Q}_0$ fit.

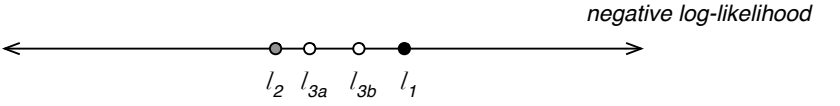
**Example.** Consider the following example, illustrating the process of choosing the best term to add to the intercept model for $g$, given $W = (W_1, W_2, W_3)$.

*C-TMLE Algorithm Example with $W = (W_1, W_2, W_3)$*

- Construct tentative candidate estimators for $g_{n,2}$:
  - $g_n^{2a}$: regress $A$ on $W_1$,
  - $g_n^{2b}$: regress $A$ on $W_2$,
  - $g_n^{2c}$: regress $A$ on $W_3$.
- Obtain each corresponding tentative candidate TMLE: $\bar{Q}_n^{2x} = \bar{Q}_n^0 + \epsilon_{2x} H^*_{g_n^{2x}}$, $x \in \{a, b, c\}$.
- Select the $x$ that minimizes the negative log-likelihood $l(\bar{Q}_n^{2x})$.
- The best TMLE is given by $\bar{Q}_n^{2b}$, and note that $l(\bar{Q}_n^{2b}) < l(\bar{Q}_n^1)$, so that we accept this choice as our next $\bar{Q}_n^2$ in the sequence of TMLEs, with corresponding $g_{n,2} = g_n^{2b}$. We now have $\bar{Q}_n^1, \bar{Q}_n^2$ and corresponding $g_{n,1}, g_{n,2}$.

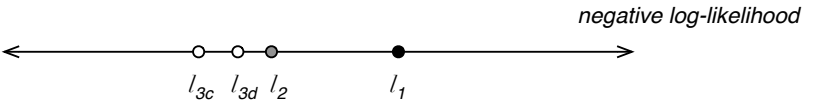



- Construct tentative candidate estimators for $g_{n,3}$:
  - $g_n^{3a}$: regress $A$ on $W_2, W_1$,
  - $g_n^{3b}$: regress $A$ on $W_2, W_3$.
- Obtain each corresponding tentative candidate TMLE: $\bar{Q}_n^{3x} = \bar{Q}_n^0 + \epsilon_{3x} H^*_{g_n^{3x}}$, $x \in \{a, b\}$.
- Select the $x$ that minimizes the negative log-likelihood $l(\bar{Q}_n^{3x})$.
- The best TMLE is given by $\bar{Q}_n^{3a}$, but note that $l(\bar{Q}_n^{3a} > l(\bar{Q}_n^2)$. Therefore, we do not accept this best TMLE as our next TMLE $\bar{Q}_n^3$ in the sequence of TMLEs.




- Instead, we update the initial in our tentative candidate TMLEs by replacing the initial $\bar{Q}_n^0$ by $\bar{Q}_n^2$, and repeat our search for $Q_n^3$ with this new initial, as follows.
- Construct tentative candidate estimators for $g_{n,3}$:
  - $g_n^{3c}$: regress $A$ on $W_2, W_1$,
  - $g_n^{3d}$: regress $A$ on $W_2, W_3$.
- Obtain each corresponding tentative candidate TMLE: $\bar{Q}_n^{3x} = \bar{Q}_n^{2*} + \epsilon_{3x} H^*_{g_n^{3x}}$, $x \in \{c, d\}$.

- Select the $x$ that minimizes the negative log-likelihood $l(\bar{Q}_n^{3x})$.
- The best TMLE is given by $\bar{Q}_n^{3c}$, and, note $l(\bar{Q}_n^{3c}) < l(\bar{Q}_n^2)$ (as it should), so that we accept this choice as our next $\bar{Q}_n^3$ in the sequence of TMLEs, with corresponding $g_{n,3} = g_n^{3c}$. We now have $\bar{Q}_n^1, \bar{Q}_n^2, \bar{Q}_n^3$ and corresponding $g_{n,1}, g_{n,2}, g_{n,3}$.




- Construct tentative candidate estimators for $g_{n,4}$:
  - $g_n^{4a}$: regress $A$ on $W_2, W_1, W_3$.
- Obtain each corresponding tentative candidate TMLE: $\bar{Q}_n^{4a} = \bar{Q}_n^{2*} + \epsilon_{4a} H^*_{g_n^{4a}}$ (only one choice).
- Select the $x$ that minimizes the negative log-likelihood $l(\bar{Q}_n^{4x})$: $x = a$.
- The best TMLE is given by $\bar{Q}_n^{4a}$, and, note $l(\bar{Q}_n^{3a}) < l(\bar{Q}_n^3)$, so that we accept this choice as our next $\bar{Q}_n^4$ in the sequence of TMLEs, with corresponding $g_{n,4} = g_n^{4a}$. The final sequence is thus given by: $\bar{Q}_n^1, \bar{Q}_n^2, \bar{Q}_n^3, \bar{Q}_n^4$, and we also have corresponding $g_{n,1}, g_{n,2}, g_{n,3}, g_{n,4}$.

**A penalized RSS to make the empirical fit of $\bar{Q}_0$ more targeted.** We have proposed to make the empirical fit of a candidate TMLE of $\bar{Q}_0$ more targeted than the empirical risk of the squared error loss function (i.e., the RSS) by adding to the RSS a penalty term proportional to the estimated variance of this candidate TMLE of the target parameter. Since this penalty is asymptotically negligible relative to RSS, this penalized RSS for a candidate TMLE of $\bar{Q}_0$ is still asymptotically minimized at the true $\bar{Q}_0$ and thereby represents a valid loss function. The variance of the candidate TMLE of the target parameter may be estimated using the empirical variance of the estimated efficient influence curve $D^*$.

Specifically, a penalized cross-validated sum of squared residuals, and the corresponding cross-validation selector of $k$ can be defined as follows. The cross-validation selector is defined as

$$k_n = \underset{k}{\operatorname{argmin}}\ \mathrm{cvRSS}_k + \mathrm{cvVar}_k + n \times \mathrm{cvBias}_k^2,$$

where these terms are given by

$$\text{cvRSS}_k = \sum_{v=1}^{V} \sum_{i \in Val(v)} (Y_i - \hat{\bar{Q}}_k^*(P_{nv}^0)(W_i, A_i))^2,$$

$$\text{cvVar}_k = \sum_{v=1}^{V} \sum_{i \in Val(v)} D^{*2}(\hat{\bar{Q}}_k^*(P_{nv}^0), \hat{g}^k(P_n), \hat{\Psi}(\hat{Q}_k^*(P_{nv}^0)))(O_i),$$

$$\text{cvBias}_k = \frac{1}{V} \sum_{v=1}^{V} \Psi(\hat{Q}_k^*(P_{nv}^0)) - \Psi(\hat{Q}_k^*(P_n)).$$

Here $v$ indexes the validation set $Val(v)$ of size $np$ and empirical distribution $P_{n,v}^0$ of the training sample of size $n(1-p)$ for the $v$th fold, $v = 1, \ldots, V$, and $p = 1/V$. For any $Q, g, D^*(Q, g, \Psi(Q))$ denotes the efficient influence curve of our target parameter at $(Q, g)$:

$$D^*(Q, g, \Psi(Q))(O) = \frac{I(A=1) - I(A=0)}{g(A \mid W)}(Y - \bar{Q}(A, W)) + \bar{Q}(1, W) - \bar{Q}(0, W) - \Psi(Q).$$

Note that the logistic regression models for $g_0$ used by $g_{n,k}$ are not restricted to the univariate components of $W$ only. For example, variables can be created that correspond to higher-order terms, such as interactions of the components of $W$. In addition, a categorical or continuous univariate covariate can be split into many binary covariates, thereby allowing for more nonparametric modeling of the effect of a single covariate. In addition, most importantly, a series of increasingly nonparametric propensity score estimates using super learning can be obtained based on different covariate sets. These super learner fits of the propensity score would then be used as the main terms in the algorithm described above. When there are many covariates, it might be desirable in practice to terminate the procedure before all covariates have been incorporated into the model for $g_0$, though care must be taken to ensure that none of the candidates thereby excluded from the subsequent selection process potentially maximizes the empirical criterion. In this manner the total number of candidates $K$ is controlled without loss of practical performance of the resulting C-TMLE.

### *19.1.1 Simulations: Estimator Comparison*

Three simulation studies illustrate the performance of the C-TMLE under different data-generating scenarios and are designed to provide insight into estimator performance under confounding of the relationship between treatment and outcome, complex underlying data-generating distributions, and practical violations of the positivity assumption. Other estimators commonly used to assess causal effects are also evaluated. A comparison of these estimators highlights the differences in their

behavior and illustrates the importance of statistical properties such as double robustness, asymptotic efficiency, and robustness in the context of sparsity.

The unadjusted estimator is defined as

$$\psi_n^{unadj} = \frac{1}{n}\sum_{i=1}^{n}(2A_i - 1)Y_i.$$

If the covariates confound the relationship between treatment and outcome, the unadjusted estimator will be biased. Given an ML-based estimator $\bar{Q}_n^0$ of $\bar{Q}_0$, the MLE of $\psi_0$ is defined as

$$\psi_n^{MLE} = \frac{1}{n}\sum_{i=1}^{n}(\bar{Q}_n^0(1, W_i) - \bar{Q}_n^0(0, W_i)).$$

This estimator is consistent if $\bar{Q}_n^0$ is a consistent estimator of $\bar{Q}_0$. The IPTW estimator is defined as

$$\psi_n^{IPTW} = \frac{1}{n}\sum_{i=1}^{n}(I(A_i = 1) - I(A_i = 0))\frac{Y_i}{g_n(A_i \mid W_i)}.$$

Large weights, practical or theoretical violation of the positivity assumption $0 < g_0(1 \mid W) < 1$, is known to make this estimator variable and biased (Freedman and Berk 2008). The A-IPTW estimator is defined as

$$\begin{aligned}\psi_n^{A-IPTW} = &\frac{1}{n}\sum_{i=1}^{n}\frac{I(A_i = 1) - I(A_i = 0)}{g_n(A_i \mid W_i)}(Y_i - \bar{Q}_n^0(A_i, W_i)) \\ &+\frac{1}{n}\sum_{i=1}^{n}(\bar{Q}_n^0(1, W_i) - \bar{Q}_n^0(0, W_i)),\end{aligned}$$

and is asymptotically unbiased and efficient when both $g_n$ and $\bar{Q}_n^0$ are asymptotically consistent estimators of $g_0$ and $\bar{Q}_0$, respectively. This estimator remains unbiased if at least one of these estimators is asymptotically consistent. Unlike C-TMLE, A-IPTW relies on external estimation of $g_0$, and may therefore include covariates that are predictive only of treatment, tending to increase both bias and variance.

The propensity score (pscore) estimator (Rosenbaum and Rubin 1983) that calculates the marginal treatment effect as the mean across strata defined by the conditional probability of receiving treatment is given by

$$\psi_n^{pscore} = \frac{1}{n}\sum_{i=1}^{n}(\bar{Q}_n^0(1, s_i) - \bar{Q}_n^0(0, s_i)),$$

where $\bar{Q}_n^0(a, s)$ is an estimator of the true conditional mean $E(Y \mid A = a, S = s)$, and $s_i$ indicates a stratum of the pscore of covariate vector $W_i$. The pscore estimator is asymptotically consistent if $g_n$ is a consistent estimator of $g_0$ and if one lets the num-

ber of strata converge to infinity as sample size increases. This will typically require a data-adaptive method for selection of the strata and the number of strata. Contrary to a nonparametric MLE based on the reduced-data structure $(g_n(1 \mid W), A, Y)$, it is commonly recommended in the literature to ignore the outcome data in the construction of these strata, even though this may heavily harm the performance of this estimator. Estimates can suffer even when overall match quality based on the pscore is high if only a small subset of the covariates are true confounders and these are unevenly distributed between treatment and control groups. Like most estimators, these are known to perform poorly when there are positivity violations (Sekhon 2008a). Because this estimator ignores covariate information and outcome data, it is known to not be asymptotically inefficient.

The matching estimator (Sekhon 2008a), an extension of pscore estimators that matches observations in treatment and control groups based on minimizing a distance between the covariates $W$ of a treated and untreated unit, is defined as

$$\psi_n^{matching} = \frac{1}{n} \sum_{i=1}^{n} (\bar{Q}_n^0(1, m_i) - \bar{Q}_n^0(0, m_i)),$$

where $\bar{Q}_n^0(a, m)$ is a nonparametric estimator of the conditional mean $E(Y \mid A = a, M = m)$, and $m_i$ indicates a set of matched observations to which subject $i$ is assigned. The matching algorithm this estimator relies upon carefully matches observations in the treatment and control groups an effort to evenly distribute potential confounders. The matching procedure relies on the genetic algorithm (Holland and Reitman 1977) to achieve this goal. Candidate sets of matches are evaluated based on a loss function and a distance metric between covariate vectors, specified at run time, and are used to generate successive sets of candidates that achieve good balance (Sekhon 2008a). The matching estimator can be provided with a pscore estimator as one of the covariates. The marginal treatment effect is the average of the empirical effects across the strata defined by the sets of matches. As with the pscore estimator, this one also ignores the outcome in the construction of the strata.

The C-TMLE is defined as

$$\psi_n^{C-TMLE} = \frac{1}{n} \sum_{i=1}^{n} (\bar{Q}_n^*(1, W_i) - \bar{Q}_n^*(0, W_i)),$$

where $\bar{Q}_n^*$ refers to an update of an initial estimator $\bar{Q}_n^0$, as described previously. Note that the unadjusted estimator, the pscore estimator, the matching estimator, the TMLE, and the C-TMLE are all substitution estimators based on plugging in an estimator of $\bar{Q}_0$, so that these estimators only differ in the manner in which $\bar{Q}_0$ is estimated.

Covariates $W_1, \ldots W_5$ are generated as independent normal random variables, while $W_6$ is a binary variable. Specifically,

$$W_1, W_2, W_3, W_4, W_5 \sim N(0, 1),$$
$$P_0(W_6 = 1 \mid W_1, W_2, W_3, W_4, W_5) = \text{expit}(0.3W_1 + 0.2W_2 - 3W_3).$$

We use the following two treatment mechanisms:

$$g_{1,0}(1 \mid W) = \text{expit}(0.3W_1 + 0.2W_2 - 3W_3)$$
$$g_{2,0}(1 \mid W) = \text{expit}(0.15 \times (0.3W_1 + 0.2W_2 - 3W_3)).$$

We also use two conditional distributions of the outcome $Y$ specified as follows:

$$Y = \bar{Q}_{i,0}(A, W) + \epsilon,\ \epsilon \sim N(0, 1),$$

with corresponding true outcome regressions:

$$\bar{Q}_{1,0}(A, W) = A + 0.5W_1 - 8W_2 + 9W_3 - 2W_5$$
$$\bar{Q}_{2,0}(A, W) = A + 0.5W_1 - 8W_2 + W_3 + 8W_3^2 - 2W_5.$$

We use three different data-generating distributions: $(\bar{Q}_{1,0}, g_{1,0})$ in simulation 1, $(\bar{Q}_{2,0}, g_{1,0})$ in simulation 2, and $(\bar{Q}_{2,0}, g_{2,0})$ in simulation 3.

Note that $W_6$ is strongly correlated with treatment $A$ in simulations 1 and 2 (corr = 0.54) but is not an actual confounder of the relationship between $A$ and $Y$. The true confounders are $W_1, W_2$, and $W_3$. The linear nature of the confounding due to $W_3$ in simulation 1 differs from that in simulations 2 and 3, where the true functional form is quadratic. In this way simulations 2 and 3 try to mimic realistic data analysis scenarios in which the unknown underlying functional form is seldom entirely captured by the regression model used in the analysis. Finally, the treatment mechanism in simulations 1 and 2 leads to positivity violations. Specifically, $P(A = 1 \mid W)$ ranges between $9 \times 10^{-7}$ and 0.9999978, and approximately one-third of the probabilities are outside the range (0.05, 0.95). In simulation 3 there are no ETA violations since $0.11 < P(A = 1 \mid W) < 0.88$. In each simulation the true value of the parameter of interest equals 1: $\psi_0 = 1$.

One thousand samples of size $n = 1000$ were drawn from each data generating distribution. A main effects model fit for $\bar{Q}_n^0$ was obtained using the data-adaptive DSA algorithm restricted to main terms only for the MLE and A-IPTW estimators. A main terms logistic regression model fit for the treatment mechanism $g_n$ was also selected by DSA, using the logistic link and restricted to main terms only, and provided as input into the IPTW, A-IPTW, pscore, and matching estimators. The pscore method was implemented by dividing observations into strata based on the five quintiles of the predicted conditional treatment probabilities. Any weights that were greater than 10 were set to 10 for the IPTW estimator.

Mean estimates of the treatment effect and standard errors for each simulation are shown in Table 19.1 and Fig. 19.1 illustrates each estimator's behavior. As expected, the estimators relying on consistent estimation of $\bar{Q}_0$ are unbiased in simulation 1, while those relying on consistent estimation of $g_0$ are unbiased in simulation 3. The unadjusted estimator yields biased results in all three simulations due to its failure to adjust for confounders. The ML-based estimator performs well in simulation 1 when the DSA estimator consistently estimates $\bar{Q}_0$. We understand that misspecification of $\bar{Q}_n^0$ (simulations 2 and 3) will often, though not always, lead to

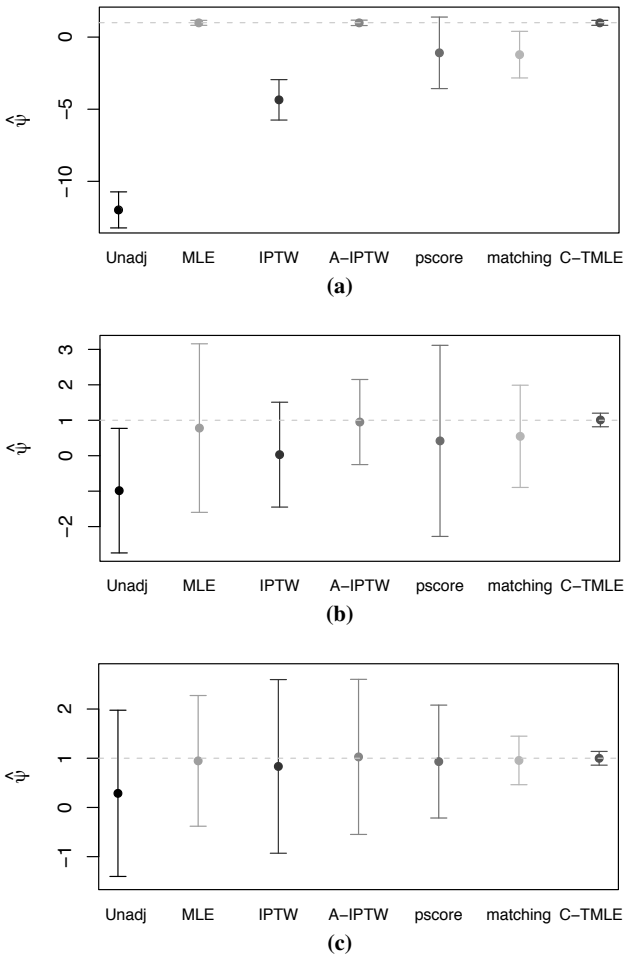



**Fig. 19.1** Means and (0.025, 0.975) quantiles. (a) Simulation 1. (b) Simulation 2. (c) Simulation 3

**Table 19.1** Means and standard errors for each estimator, 1000 iterations, $n = 1000$, $\psi_0 = 1$

| | Simulation 1 | | Simulation 2 | | Simulation 3 | |
|---|---|---|---|---|---|---|
| | $\psi_n$ | SE | $\psi_n$ | SE | $\psi_n$ | SE |
| Unadj | −11.97 | 0.64 | −0.98 | 0.91 | 0.29 | 0.86 |
| MLE | 0.99 | 0.09 | 0.76 | 1.22 | 0.95 | 0.68 |
| IPTW | −4.36 | 0.72 | 0.03 | 0.76 | 0.83 | 0.90 |
| A-IPTW | 0.99 | 0.09 | 0.94 | 0.62 | 1.03 | 0.80 |
| pscore | −1.09 | 1.27 | 0.42 | 1.38 | 0.93 | 0.59 |
| matching | −1.22 | 0.82 | 0.54 | 0.73 | 0.96 | 0.25 |
| C-TMLE | 0.99 | 0.09 | 1.00 | 0.10 | 1.00 | 0.07 |

bias in the estimates. However, the plots highlight another phenomenon that is easy to overlook. The inability of the misspecified regression fit to explain the variance in the outcome often leads to large variance of the estimator of the treatment effect $\psi_0$. Truncation bias due to positivity violations causes the IPTW estimator using truncated weights to fail in simulations 1 and 2. The estimate is not biased in simulation 3, but the variance is so large that even in this setting where we'd expect IPTW to be reliable it fails to produce a significant result. A-IPTW estimates are unbiased and have low variance when the DSA algorithm selects the right model fit of $\bar{Q}_0$ (simulation 1). However, the variance of the A-IPTW estimator is large in simulations 2 and 3 because, despite not being a confounder, $W_6$, a strong predictor of $A$, is always included in the estimate of the treatment mechanism, thus needlessly increasing the variance.

The pscore has poor performance in simulations 1 and 2 when there are positivity violations. Without using information about the outcome the fit of the pscore can be based on the predictive power of the fit, but not on the potential bias reduction. The pscore method does a reasonable job in simulation 3. The matching estimator performs quite well; however, it is quite inefficient in simulation 1.

These simulation studies demonstrate the collaborative double robustness and efficiency of C-TMLE methodology, which allows for consistent efficient estimation in situations where other estimators can fail to perform adequately. In practice these failures may lead to biased estimates and to confidence intervals that fail to attain the correct coverage, as suggested by the IPTW results in simulations 1 and 2, where weights depend on a variable highly predictive of treatment that is not a true confounder of the relationship between $Y$ and $A$.

As simulations 2 and 3 demonstrate, a misspecified parametric model not only results in biased estimates, but can also easily fail to adequately explain the variance in the outcome. Therefore maximum likelihood estimates of the parameter of interest based on such misspecified parametric models may have a larger variance than the semiparametric information bound achieved by an efficient estimator, such as a C-TMLE.

Estimators that rely on ML-based estimators of the treatment mechanism (IPTW, A-IPTW, TMLE, pscore) break down when there are positivity violations, failing to reduce bias, or even increasing bias, while incurring high variance that renders estimates meaningless (no statistical significance). An effort to reduce variance through truncation introduces bias into the estimate, and requires a careful tradeoff. C-TMLE addresses these issues, in the sense that it is able to utilize the covariates for effective bias reduction, avoiding harmful bias reduction efforts, reflected by the inclusion of $W_6$ in the treatment mechanism estimator.

To summarize, the collaborative nature of the estimation of the treatment mechanism in the C-TMLE confers three advantages:

1. The treatment mechanism model will exclude covariates that are highly predictive of treatment but do not truly confound the relationship between treatment and outcome.
2. The treatment mechanism model will strongly favor inclusion of covariates that help adjust for residual bias remaining after the initial estimator.
3. By employing the penalized RSS in the C-TMLE algorithm, the procedure will not select a treatment mechanism model that includes a term that leads to strong violations of the positivity assumption and thereby large variance of the corresponding TMLE without the benefit of a meaningful bias reduction.

### *19.1.2 Simulations: Comparison of C-TMLE and TMLE*

The double robust property of TMLE minimizes the need for accurate estimation of both $\bar{Q}_0$ and $g_0$ since correct specification of either one leads to consistent estimates of the parameter of interest. However, accurate estimates of both are needed to achieve the Cramer–Rao efficiency bound. Implementations of the standard TMLE therefore strive for ideal estimates of both $\bar{Q}_0$ and $g_0$.

In contrast, the collaborative nature of the second stage of the C-TMLE algorithm leads to selection of an estimator, $g_n$, that targets that portion of the treatment mechanism needed to reduce bias not already adequately addressed by the initial estimator $\bar{Q}_n^0$ of $\bar{Q}_0$. For example, covariates included in the model fit $\bar{Q}_n^0$ might not be selected into the model fit for $g_0$ because they do not decrease the penalized RSS. At the same time, confounders that are not adequately adjusted for in the initial estimator $\bar{Q}_n^0$ are quickly added to model for $g_0$ unless the gain in bias reduction is offset by too great an increase in variance. When the initial estimate $\bar{Q}_n^0$ is a very good fit of $\bar{Q}_0$, the TMLE and C-TMLE have similar performance with respect to bias, but the C-TMLE may have a smaller finite sample variance by selecting a $g_n$ that targets a non-fully-adjusted true conditional distribution of treatment, resulting in a possibly super efficient estimator. When the initial fit is less good, C-TMLE makes informed choices regarding inclusion of covariates in the treatment mechanism. As predicted by theory, again, this might lead to lower finite sample variances and more effective bias reduction.

The following simulation 4 illustrates these phenomena and shows the breakdown of the TMLE using the squared error loss function and linear fluctuation in the presence sparsity. The covariates $W_1, W_2$, and $W_3$ are generated as independent random uniform variables over the interval $[0, 1]$, while $W_4$ and $W_5$ are independent normally distributed random variables. Specifically,

$$\begin{aligned} W_1, W_2, W_3 &\sim U(0, 1), \\ W_4, W_5 &\sim N(0, 1). \end{aligned}$$

The treatment mechanism $g_0$ is designed so that $W_3$ is highly predictive of treatment:

$$g_0 = P_0(A = 1 \mid W) = \text{expit}(2W_1 + W_2 - 5W_3 + W_5).$$

The observed outcome $Y$ is generated as:

$$Y = A + 4W_1 - 5W_2 + 5W_4W_5 + \epsilon,\ \epsilon \sim N(0, 1).$$

The true causal effect $\psi_0$ equals 1.

C-TMLE and TMLE of $\psi_0$ were obtained for 1000 samples of size $n = 1000$ drawn from data-generating distribution implied by $(Q_0, g_0)$. For this study we deliberately selected a misspecified main-terms-only model for $\bar{Q}_0$ by running the DSA algorithm restricted to main terms only. The propensity score $P(A = 1 \mid W)$ ranges from 0.004 to 0.996. Approximately 17% of the propensity scores are smaller than 0.05, indicating that practical positivity violations in finite samples cause the TMLE to be unstable.

We expect that the initial estimator of $\psi_0$ based on the misspecified $\bar{Q}_n^0$ (that excludes the interaction term) is biased. The targeting step for both targeted estimators are supposed to reduce this bias. The treatment mechanism $g_0$ is estimated with the DSA algorithm, allowing for quadratic terms and two-way interactions. The covariates that were candidates for inclusion in the model for $g_n$ in the C-TMLE algorithm include $(W_1, \ldots, W_5, W_1^2, \ldots, W_5^2)$ and all two-way interaction terms $(W_i \times W_j)$ with $i \neq j$.

Results of the simulation are shown in Table 19.2. A small number of aberrant realizations of the TMLE were major contributors to the variance of that estimator. The three highest TMLEs of the treatment effect were 771.91, 37.22, and 9.52. It is likely that these high values arise from atypical samples containing observations that presented unusually strong positivity issues. In contrast, all C-TMLEs calculated from the same samples range from 0.307 to 1.698. Both estimators' average treatment effect estimates are not far from the true value, $\psi_0 = 1$. As expected, the variance of the TMLE is many times larger than that of the C-TMLE.

Not surprisingly, $W_3$, the strong predictor of treatment that is not a true confounder of the relationship between treatment and outcome, is included in every one of the 1000 models for $g_n$ selected by the DSA algorithm, but it is included in only 35 of the models constructed in the estimator $g_n$ selected by the C-TMLE

**Table 19.2** Means and variance for each estimator, 1000 iterations, $n = 1000$, $\psi_0 = 1$

| | Truncation level | # Obs truncated | $\psi_n$ | Variance |
|---|---|---|---|---|
| C-TMLE | $\infty$ | 0 | 0.98 | 0.04 |
| TMLE | $\infty$ | 0 | 1.73 | 597.52 |
| | 40 | 1 | 1.36 | 162.38 |
| | 10 | 2 | 0.94 | 1.99 |
| | 5 | 9 | 0.92 | 1.68 |

algorithm. At the same time, the interaction term $W_4 \times W_5$ is included in only two out of 1000 model fits for $g_0$ selected by DSA but is present in 576, more than half, of the estimators $g_n$ selected by the C-TMLE.

This demonstrates the differences between the reliance of TMLE on an external estimate of $g_0$ and the collaborative approach to estimating the treatment mechanism used by C-TMLE. However, we note that the lack of robustness of the TMLE performance under sparsity is due to the unboundedness of the fluctuation function, and can be mitigated by employing the logistic fluctuation function (Chap. 7) that respects known bounds. These results were previously demonstrated for the TMLE and will also be demonstrated for the C-TMLE in a later section of this chapter.

### *19.1.3 Data Analysis*

We apply the C-TMLE to an observational data set previously analyzed with the goal of identifying HIV mutations that affect response to the antiretroviral drug lopinavir (Bembom et al. 2008, 2009). For each analysis, which aims to assess the effect of one mutation $A$ among the 26 mutations, the data structure on one subject can be represented as $O = (W, A, Y)$, where the outcome, $Y$, is the change in $\log_{10}$ viral load measured at baseline and at follow-up after treatment has been initiated, and $W$ denotes the other 25 mutations and other summary measures of the history of the patient at baseline. If follow-up viral load was beneath the limit of detection, then $Y$ was set to the maximal change seen in the population. Here $A \in \{0, 1\}$ is an indicator of the presence or absence of the mutation of interest. The covariate vector $W$ consists of 51 covariates including treatment history, baseline characteristics, and indicators of the presence of additional HIV mutations. Practical positivity violations stemming from low probabilities of observing a given mutation of interest, given the other covariates, make it difficult to obtain a stable low variance estimate of the additive effect of $A$ on the mean of $Y$, defined as $E_0[\bar{Q}_0(1, W) - \bar{Q}_0(0, W)]$.

Bembom et al. used a TMLE approach incorporating data-adaptive selection of an adjustment set (subset of $W$). Covariates whose inclusion in the adjustment set introduces an unacceptable amount of estimated bias were not selected. That study found substantial agreement with Stanford HIVdb mutation scores, values on a scale of 0 to 20 (http://hivdb.stanford.edu, as of September 2007, subsequently modified), where 20 indicates evidence exists that the mutation strongly inhibits response to drug treatment and 0 signifies that the mutation confers no resistance. Because the C-TMLE method includes covariates in the treatment mechanism only if they improve the targeting of the parameter of interest without having too much of an adverse effect on the MSE, we expect similar performance without having to specify an acceptable maximum amount of estimated bias.

The data set consists of 401 observations on 372 subjects. A C-TMLE of the additive effect of the mutation on change in viral load was carried out for each mutation. In each, a regression estimator $\bar{Q}_n^0$, was obtained using the DSA algorithm restricted to addition moves only, main terms only, and a maximum of 20 terms,

where candidate terms in $W$ include precomputed interactions detailed in Bembom et al. The mutation itself, $A$, was forced into the model fit of the DSA. Influence-curve-based variance estimates incorporating the contribution from estimating $g_0$ were used to construct 95% confidence intervals as detailed in Gruber and van der Laan (2010a).

Table 19.3 lists the Stanford mutation score associated with each of the HIV mutations under consideration, as well as the C-TMLE of the adjusted effect of mutation on lopinavir resistance. Confidence intervals entirely above zero indicate a mutation increases resistance to lopinavir. Eight of the twelve mutations having a mutation score of 10 or greater fall into this category. Point estimates for the remaining four mutations were positive, but the variance was too large to produce a significant result. Only one of the six mutations thought to confer slight resistance to lopinavir was flagged by the procedure, though, with the exception of p10FIRVY, point estimates were positive. Stanford mutation scores of 0 for four of the five mutations found to have a significantly negative effect on drug resistance support the conclusion that these mutations do not increase resistance, but are not designed to

**Table 19.3** Stanford score (2007), C-TMLE estimate, and 95% confidence interval for each mutation. Starred confidence intervals do not include 0

| Mutation | Score | Estimate | 95% CI |
|---|---|---|---|
| p50V | 20 | 1.703 | (0.760, 2.645)* |
| p82AFST | 20 | 0.389 | (0.091, 0.688)* |
| p54VA | 11 | 0.505 | (0.241, 0.770)* |
| p54LMST | 11 | 0.369 | (0.002, 0.735)* |
| p84AV | 11 | 0.099 | (−0.139, 0.337) |
| p46ILV | 11 | 0.046 | (−0.222, 0.315) |
| p82MLC | 10 | 1.610 | (1.377, 1.843)* |
| p47V | 10 | 0.805 | (0.282, 1.328)* |
| p84C | 10 | 0.602 | (0.471, 0.734)* |
| p32I | 10 | 0.544 | (0.325, 0.763)* |
| p48VM | 10 | 0.306 | (−0.162, 0.774) |
| p90M | 10 | 0.209 | (−0.063, 0.481) |
| p33F | 5 | 0.300 | (−0.070, 0.669) |
| p53LY | 3 | 0.214 | (−0.266, 0.695) |
| p73CSTA | 2 | 0.635 | (0.278, 0.992)* |
| p24IF | 2 | 0.229 | (−0.215, 0.674) |
| p10FIRVY | 2 | −0.266 | (−0.545, 0.012) |
| p71TVI | 2 | 0.019 | (−0.243, 0.281) |
| p23I | 0 | 0.822 | (−0.014, 1.658) |
| p36ILVTA | 0 | 0.272 | (−0.001, 0.544) |
| p16E | 0 | 0.239 | (−0.156, 0.633) |
| p20IMRTVL | 0 | 0.178 | (−0.111, 0.467) |
| p63P | 0 | −0.131 | (−0.417, 0.156) |
| p88DTG | 0 | −0.426 | (−0.842,−0.010)* |
| p30N | 0 | −0.440 | (−0.853,−0.028)* |
| p88S | 0 | −0.474 | (−0.781,−0.167)* |

offer confirmation that a mutation can decrease drug resistance. However, Bembom et al. report that there is some clinical evidence that two of these mutations, 30N and 88S, do indeed decrease lopinavir resistance. These findings are consistent with the Stanford mutation scores and with the results from the previous analysis using the data-adaptively selected adjustment set TMLE approach.

## 19.2 Logistic Fluctuation for Bounded Continuous Outcomes

Chapter 7 described the importance of using a fluctuation working model in the TMLE procedure that respects the global constraints of the model. We introduced a logistic fluctuation procedure that ensures the TMLE of $\bar{Q}_0(A, W)$ remain within the bounds of the semiparametric model. This is especially relevant in sparse data situations, when outlying values for $Y$ or $\bar{Q}_0(A, W)$ or extreme conditional treatment assignment probabilities inflate the variance of the efficient influence curve of the parameter of interest. An analysis of simulated data illustrates that employing a logistic fluctuation of $\bar{Q}_n^0$ in the targeting steps of the C-TMLE procedure further robustifies the C-TMLE under sparsity relative to the C-TMLE using the linear fluctuation function.

The targeting step of the TMLE procedure for a binary outcome uses logistic regression of $Y$ on $H^*(A, W)$ with offset $\text{logit}(\bar{Q}_n^0)$ to fit its regression parameter $\epsilon$, a parameter that dictates the magnitude of the fluctuation of the initial estimate. This naturally constrains the updated estimate, $\bar{Q}_n^1(A, W) = \text{expit}(\text{logit}(\bar{Q}_n^0(A, W)) + \epsilon H^*(A, W))$, to be between 0 and 1. If, instead, $Y$ represents a continuous outcome known to be bounded between (0,1), for example, a proportion, then it is equally true that this same logistic regression updating algorithm, ignoring that $Y$ is not binary, yields fitted values for $Y$ that fall between 0 and 1.

Now suppose there is instead a continuous outcome $Y$ known to be bounded by $(a, b)$, with $a < b$. Ideally, an estimate of the conditional mean of $Y$ given $A$ and $W$ should remain within $[a, b]$. We've just seen that this is easily arranged when $(a, b) = (0, 1)$. For arbitrary $(a, b)$, $Y \in [a, b]$ can be mapped to $Y^* = (Y - a)/(b - a) \in [0, 1]$. We can then define the causal effect of treatment on the bounded outcome $Y^*$ as $\Psi^*(P_0) = E_0[E_0(Y^* \mid A = 1, W) - E_0(Y^* \mid A = 0, W)]$. The same C-TMLE procedure outlined in Sect. 19.1 is applied to the data structure $O^* = (W, A, Y^*)$ to obtain an estimate $\psi_n^*$, but now using the logistic fluctuation (instead of linear) and the (possibly penalized) log-likelihood of a binary $Y^*$, given $(W, A)$, as loss function for $\bar{Q}_0$ (instead of squared error loss function). This C-TMLE $\psi_n^*$ immediately maps to a $\psi_n$ of the causal effect on the original scale, using the relation $\Psi(P_0) = (b - a)\Psi^*(P_0)$. A confidence interval for $\psi_0$ can be obtained by multiplying the bounds on the confidence interval for $\Psi^*(P_0)$ by $(b - a)$. Similarly, the estimated variance $\hat{\sigma}^2$ of $\psi_n$ is obtained by multiplying the estimated variance $\hat{\sigma}^{2*}$ of $\psi_n^*$ with$(b - a)^2$.

### *19.2.1 Simulations: Logistic vs. Linear Fluctuation*

The random variables were generated as follows:

$$W_1, W_2, W_3 \sim N(\mu_1, \mu_2, \mu_3, \Sigma),\ \mu_1 = \mu_2 = \mu_3 = 0,\ \ \Sigma = \begin{bmatrix} 2 & 1 & 0 \\ 1 & 1 & 0.2 \\ 0 & 0.2 & 1 \end{bmatrix},$$
$$W_4 \sim Bernoulli(0.2),$$
$$W_5 \sim Bernoulli(0.6),$$
$$W_6 \sim Bernoulli(0.7).$$

The treatment mechanism $g_0$ is given by $g_0 = P_0(A = 1 \mid W) = \text{expit}(2W_1 + 0.25W_2 - 0.5W_3 + W_4)$. The observed outcome $Y$ is generated as $Y = A + 2A \times W_5 + W_1 + W_2 - W_3 \times W_5 + \epsilon$, $\epsilon \sim N(0, 1)$. Notice that the covariates $(W_1, W_2, W_3, W_4)$ are causally related to treatment. The covariates $W_1, W_2$, and $W_3$ are also causally related to the outcome, and therefore confound the relationship between treatment and the outcome. Covariate $W_6$ was measured at baseline, but has no association with either the treatment or the outcome. Covariate $W_5$ is an effect modifier. The effect of treatment is larger for subjects having $W_5 = 1$ than for subjects having $W_5 = 0$. Though approximately one-half of the subjects receive treatment [$P_0(A = 1) = 0.53$ marginally], true treatment assignment probabilities vary between (0.0002, 0.9999), and for approx. 9% of observations the conditional probability of receiving treatment given the measured covariates is outside (0.05, 0.95). We drew 1000 samples of size $n = 1000$ from this data-generating distribution. Observed values for $Y$ and fitted values $\bar{Q}_n^0$ of the conditional mean $\bar{Q}_0$ were truncated at the (0.01, 0.99)-quantiles of the marginal distribution of $Y$, given by (−5.83, 8.48). The true value of the marginal additive treatment effect on the bounded outcome $Y$ is $\psi_0 = 2.192$.

Two C-TMLEs were applied to estimate the additive causal effect: C-TMLE$_{log}$, using a logistic fluctuation, and C-TMLE$_{lin}$, using a linear fluctuation. In order to demonstrate the impact the targeting step has on reducing bias, $\bar{Q}_n^0$ was obtained in

**Table 19.4** Comparison of C-TMLE$_{log}$ and C-TMLE$_{lin}$, $\psi_0 = 2.192$

| | $\bar{Q}$ correctly specified | | | | $\bar{Q}$ misspecified | | | |
|---|---|---|---|---|---|---|---|---|
| | $\psi_n$ | Bias | Var | MSE | $\psi_n$ | Bias | Var | MSE |
| $g_n$ bound = 0 | | | | | | | | |
| C-TMLE$_{log}$ | 2.222 | 0.030 | 0.008 | 0.009 | 2.154 | −0.038 | 0.033 | 0.034 |
| C-TMLE$_{lin}$ | 2.221 | 0.029 | 0.008 | 0.009 | 1.992 | −0.200 | 0.349 | 0.389 |
| $g_n$ bound = 0.01 | | | | | | | | |
| C-TMLE$_{log}$ | 2.222 | 0.030 | 0.008 | 0.009 | 2.151 | −0.041 | 0.032 | 0.034 |
| C-TMLE$_{lin}$ | 2.221 | 0.029 | 0.008 | 0.009 | 2.057 | −0.135 | 0.297 | 0.315 |
| $g_n$ bound = 0.025 | | | | | | | | |
| C-TMLE$_{log}$ | 2.222 | 0.030 | 0.008 | 0.009 | 2.146 | −0.046 | 0.027 | 0.029 |
| C-TMLE$_{lin}$ | 2.221 | 0.029 | 0.008 | 0.009 | 2.116 | −0.076 | 0.054 | 0.060 |

two ways: (1) using the correct parametric regression model and (2) using a misspecified parametric regression model that assumes a univariate regression of $Y$ on $A$ only. Results in Table 19.4 illustrate that, as expected, when the model for $\bar{Q}_n^0$ is correctly specified, there is little difference between fluctuating on the logistic or linear scale.

Differences emerge when the model for $\bar{Q}_n^0$ is misspecified. At each level of bound on $g_n$, the linear fluctuation yields estimates that are much more biased and have higher variance than the logistic fluctuation-based estimates. Increasing the bound on $g_n$ from 0 to 0.025 reduces both bias and variance for the linear fluctuation estimates, but imposes a bias–variance tradeoff on the logistic fluctuation estimates. In this simulation the MSE is smaller when $g_n$ is bounded at (0.025,0.975) than when the bounds are closer to (0,1), but this is not always the case.

### *19.2.2 Simulations: Estimator Comparison*

We implemented the estimators discussed in Sect. 19.1.1, the TMLE, and C-TMLE, both using the logistic fluctuation, of the additive treatment effect under the data-generating distribution scheme for the simulation given in Sect. 19.2.1. The treatment mechanism $g_n(A \mid W)$ was bounded from below at $\{0, 0.01, 0.025\}$. Table 19.5 displays the results.

These results indicate that when the parametric model for $\bar{Q}_0$ is correctly specified, estimators that rely on consistent estimation of $\bar{Q}_0$ perform very well. However, estimators that rely only on consistent estimation of $g_0$ and fail to exploit the information from estimation of $\bar{Q}_0$ (i.e., IPTW, pscore, and matching) are less efficient, in spite of being given the correct model for $g_0$. Misspecifying the model for $\bar{Q}_0$ does not harm these estimators, but in situations like the one in this simulation, they are still less efficient than TMLE and C-TMLE.

The unadjusted estimate is biased due to confounding by covariates $W_1, W_2, W_3$. The MLE has the smallest mean squared error when the ML-based estimator of $\bar{Q}_0$ is correctly specified, but it is not robust to misspecification. The IPTW estimator, A-IPTW estimator, matching estimator, TMLE, and C-TMLE, all of which rely on an estimator $g_n$, show improvements in MSE as the bounds on $g_n$ increase from 0 to 0.025 due to a decrease in the variance at the cost of increasing bias. The IPTW estimator is consistent but very inefficient. The A-IPTW estimator has lower bias than IPTW but pays a high price in variance when $\bar{Q}_n^0$ is heavily misspecified. The pscore estimator is quite stable across all truncation levels for $g_n$; however, its lack of data adaptiveness yields an estimate that is quite biased in comparison with the other methods. The matching estimator is less biased than pscore and also quite stable with respect to changes in the bounds on $g_n$. The MSE of the matching estimator is slightly smaller than the MSE of TMLE when $\bar{Q}_n^0$ is inconsistent and approximately the same as the MSE of the C-TMLE, but the matching estimate is more biased than either TMLE or C-TMLE. Both the TMLE and C-TMLE are able to exploit information that is unavailable to the matching algorithm when $\bar{Q}_n^0$

**Table 19.5** Comparison of all estimators, $\psi_0 = 2.192$

| | $\bar{Q}$ correctly specified | | | | | $\bar{Q}$ misspecified | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $\psi_n$ | Bias | Var | MSE | RE | $\psi_n$ | Bias | Var | MSE | RE |
| $g_n$ bound = 0 | | | | | | | | | | |
| Unadj | 4.590 | 2.398 | 0.021 | 5.771 | – | 4.590 | 2.398 | 0.021 | 5.771 | – |
| MLE | 2.222 | 0.031 | 0.007 | 0.008 | 0.001 | 4.590 | 2.398 | 0.021 | 5.771 | 1.000 |
| IPTW | 2.210 | 0.018 | 0.090 | 0.090 | 0.016 | 2.210 | 0.018 | 0.090 | 0.090 | 0.016 |
| A-IPTW | 2.186 | −0.006 | 0.011 | 0.011 | 0.002 | 2.193 | 0.001 | 0.157 | 0.157 | 0.027 |
| pscore | 2.454 | 0.262 | 0.014 | 0.083 | 0.014 | 2.454 | 0.262 | 0.014 | 0.083 | 0.014 |
| matching | 2.316 | 0.124 | 0.018 | 0.033 | 0.006 | 2.316 | 0.124 | 0.018 | 0.033 | 0.006 |
| TMLE | 2.185 | −0.007 | 0.011 | 0.011 | 0.002 | 2.174 | −0.018 | 0.049 | 0.049 | 0.008 |
| C-TMLE | 2.222 | 0.030 | 0.008 | 0.009 | 0.002 | 2.154 | −0.038 | 0.033 | 0.034 | 0.006 |
| $g_n$ bound = 0.01 | | | | | | | | | | |
| Unadj | 4.590 | 2.398 | 0.021 | 5.771 | – | 4.590 | 2.398 | 0.021 | 5.771 | – |
| MLE | 2.222 | 0.031 | 0.007 | 0.008 | 0.001 | 4.590 | 2.398 | 0.021 | 5.771 | 1.000 |
| IPTW | 2.225 | 0.033 | 0.063 | 0.064 | 0.011 | 2.225 | 0.033 | 0.063 | 0.064 | 0.011 |
| A-IPTW | 2.187 | −0.005 | 0.011 | 0.011 | 0.002 | 2.216 | 0.024 | 0.092 | 0.093 | 0.016 |
| pscore | 2.454 | 0.262 | 0.014 | 0.083 | 0.014 | 2.454 | 0.262 | 0.014 | 0.083 | 0.014 |
| matching | 2.317 | 0.125 | 0.018 | 0.033 | 0.006 | 2.317 | 0.125 | 0.018 | 0.033 | 0.006 |
| TMLE | 2.185 | −0.006 | 0.011 | 0.011 | 0.002 | 2.168 | −0.024 | 0.044 | 0.044 | 0.008 |
| C-TMLE | 2.222 | 0.030 | 0.008 | 0.009 | 0.002 | 2.151 | −0.041 | 0.032 | 0.034 | 0.006 |
| $g_n$ bound = 0.025 | | | | | | | | | | |
| Unadj | 4.590 | 2.398 | 0.021 | 5.771 | – | 4.590 | 2.398 | 0.021 | 5.771 | – |
| MLE | 2.222 | 0.031 | 0.007 | 0.008 | 0.001 | 4.590 | 2.398 | 0.021 | 5.771 | 1.000 |
| IPTW | 2.277 | 0.085 | 0.041 | 0.049 | 0.008 | 2.277 | 0.085 | 0.041 | 0.049 | 0.008 |
| A-IPTW | 2.188 | −0.004 | 0.010 | 0.010 | 0.002 | 2.285 | 0.093 | 0.055 | 0.064 | 0.011 |
| pscore | 2.454 | 0.262 | 0.014 | 0.083 | 0.014 | 2.454 | 0.262 | 0.014 | 0.083 | 0.014 |
| matching | 2.319 | 0.127 | 0.018 | 0.034 | 0.006 | 2.319 | 0.127 | 0.018 | 0.034 | 0.006 |
| TMLE | 2.187 | −0.005 | 0.010 | 0.010 | 0.002 | 2.152 | −0.040 | 0.031 | 0.032 | 0.006 |
| C-TMLE | 2.222 | 0.030 | 0.008 | 0.009 | 0.002 | 2.146 | −0.046 | 0.027 | 0.029 | 0.005 |

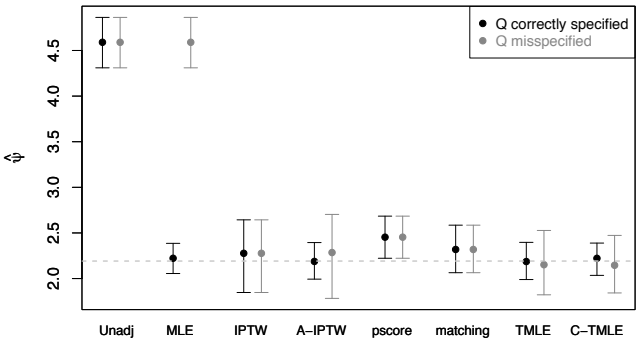



**Fig. 19.2** Means and (0.025, 0.975)-quantiles, with $g_n(1 \mid W)$ bounded at (0.025, 0.975), and the parametric model for $\bar{Q}_0$ correctly specified (*left*) and misspecified (*right*)

is consistent, and thus have lower bias and variance than the matching estimator. These results also indicate that C-TMLE may trade off a small increase in bias for a larger reduction in variance, relative to TMLE, thereby minimizing overall MSE.

The MSE provides only one of several points of comparison for estimators. Minimizing MSE is an important goal, and, as we just observed, C-TMLE can make a beneficial data-adaptive tradeoff between bias and variance, but Fig. 19.2 illustrates that an estimator with a significant bias relative to the standard error, but good MSE, such as the pscore estimator, can be problematic. The plot in Fig. 19.2 shows the mean and (0.025, 0.975)-quantiles of the estimates obtained from the 1000 generated samples. 91% of the pscore estimates were larger than $\psi_0$. This suggests that, though an estimate far from the null with a tight confidence interval may look convincing, it might in fact be misleading, and that confidence intervals for the pscore estimator might fail to achieve the nominal coverage rate under circumstances resembling those found in this simulation. This is in marked contrast to the TMLE and C-TMLE, double robust efficient substitution estimators that have desirable properties across a range of data-generating distributions.

## 19.3 Discussion

The sparsity in the data with respect to the target parameter of interest, as often induced by the high dimension of covariate profiles and lack of firm knowledge about the data-generating distribution, demands estimators that carry out a very careful bias–variance tradeoff when making decisions. Estimators that are asymptotically efficient under regularity conditions may still show a very different practical performance under sparsity. For that purpose, it is important that an efficient estimator also be a substitution estimator, based on substituting an estimator that respects the global bounds on the statistical model. In addition, the estimator of the nuisance parameter used by such an efficient estimator will need to be evaluated by its effectiveness in achieving bias reduction at the cost of a reasonable increase in variance. Using an estimator of the nuisance parameter that is blinded from this benchmark will generally not result in good estimators of the target parameter under sparsity. C-TMLE using the logistic fluctuation is an asymptotically efficient substitution estimator that also targets fitting of the nuisance parameter toward its goal. Simulations demonstrate that, under sparsity, the C-TMLE indeed outperforms other efficient estimators that either ignore global bounds or contraints or use blinded estimators of the nuisance parameter.