

## Chapter 20

# C-TMLE for Time-to-Event Outcomes

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In this chapter, the C-TMLE for the treatment-specific survival curve based on right-censored data will be presented. It is common that one wishes to assess the effect of a treatment or exposure on the time it takes for an event to occur based on an observational database. Chapters 17 and 18 discussed the treatment-specific survival curve in RCTs. The TMLE presented there improves upon common methods for analyzing time-to-event data in robustness, efficiency, and interpretability of parameter estimates. Observational data differ from RCTs in that the exposure/treatment is not set according to a known mechanism. Moreover, in situations where there is dependent censoring the censoring mechanism is also unknown. As a consequence, in observational studies, the TMLE needs to estimate the treatment and censoring mechanism, and this needs to be done in such a way that the resulting targeted bias reduction carried out by the TMLE is fully effective.

The C-TMLE, introduced in the previous chapter, is an extension of TMLE specific to situations where treatment is not randomized or censoring is informative. The C-TMLE is often more efficient for finite samples and in observational data than a standard TMLE and all other available estimators. In fact, in some instances, the C-TMLE is asymptotically super efficient in the sense that its asymptotic variance improves on the semiparametric efficiency bound for regular estimators. Furthermore, the C-TMLE is a well-behaved estimator in situations where the parameter of interest is borderline identifiable.

When exposure is not randomized there may be strata defined by baseline characteristics that never experience a particular level of exposure. This phenomenon, discussed throughout this text and in detail in Chap. 10, is a violation of the positivity assumption. Violations of the positivity assumption render the parameters of interest as presented in Chaps. 17 and 18 unidentifiable. However, many times, in finite samples, certain parameters are weakly identifiable due to practical violations of the positivity assumption. Practical violations occur when a certain value of baseline covariates are almost completely predictive of a certain treatment within the sample. C-TMLE addresses this issue and represents a stable estimator of borderline identifiable parameters. Thus, the C-TMLE methodology may be applied in

the time-to-event setting to gain efficiency as well as produce estimators of weakly identifiable parameters of interest. Readers will benefit from reading Chaps. 17–19, in addition to Part I before tackling this chapter, which is adapted from Stitelman and van der Laan (2010).

## 20.1 Estimating Parameters Based on Coarsened Data

We briefly introduce the parameter estimation problem for a general coarsened data structure. Coarsened data structures are data structures where the full data are not observed. Right-censored data structures are an example of a coarsened data structure since the full data absent right censoring are not observed. Collaborative targeted methods for estimating parameters with this data structure will be introduced.

Suppose one observes a censored data structure  $O = \Phi(C, X)$  of the full data  $X$  and censoring variable  $C$ , where  $O$  has a probability distribution  $P_0$ . Let  $\mathcal{M}$  be a semiparametric model for the probability distribution  $P_0$ . To minimize notation, we will assume  $O$  is discrete so that  $P_0(o) = P_0(O = o)$  denotes a probability density. By assuming that the conditional distribution of  $O$ , given  $X$ , satisfies the CAR assumption, the density factorizes as  $P_0(O) = Q_0(O)g_0(O | X)$ , where  $Q_0$  is the part of the density associated with the full data  $X$  and  $g_0$  is the conditional distribution of the observed data  $O$  given the full data  $X$ . Here  $C$  may encode both treatment and censoring variables, so that  $g_0$  includes both the censoring and treatment mechanisms, both of which act to coarsen the full data. The factorization of the probability density  $P_0$  implies that the model  $\mathcal{M}$  for  $P_0$  may be partitioned into a model  $\mathcal{Q}$  for  $Q_0$  and model  $\mathcal{G}$  for  $g_0$ . The probability distribution,  $P_0$ , may be indexed in the following way:  $P_{Q_0, g_0}$ . One is typically interested in estimating a parameter,  $\Psi(P_0)$ , which is a function of the true data-generating distribution. More specifically, the parameter of interest is often a function of the true full-data-generating distribution absent coarsening, and can thus be represented as  $\Psi(Q_0)$ .

Many methods have been developed to estimate  $\Psi(Q_0)$ . The MLE approach has been discussed throughout this text, and its use in time-to-event data structures is presented in Chap. 18. An alternative method for estimating  $\Psi(Q_0)$  is the IPCW-based approach, originally proposed by Koul et al. (1981) and Keiding et al. (1989). IPCW estimators solve an estimating equation in order to yield estimates,  $\psi_n^{IPCW}$ , of the parameter of interest, and  $\psi_n^{IPCW}$  is a consistent estimator of  $\Psi(Q_0)$  if the estimator of the  $g_0$ -factor is consistent. However, an IPCW estimator is ad hoc and unstable because (1) it does not solve the efficient influence curve estimating equation and is therefore generally inefficient and (2) it is not a substitution estimator and therefore does not respect the global restraints of the observed data model. As a result, an IPCW estimator is highly variable, very sensitive to the choice of estimator of  $g_0$ , and may act erratically in finite samples.

Another method for estimating  $\Psi(Q_0)$  is an A-IPCW estimator. As discussed earlier in this text, Robins and Rotnitzky (1992) proposed this general estimating-equation-based approach, which constructs estimators  $\psi_n^{A-IPCW}$  that solve the effi-

cient influence curve estimating equation. An A-IPCW estimator is double robust because it is consistent when either  $Q_0$  or  $g_0$  is estimated consistently. Furthermore, an A-IPCW estimator also improves on the standard IPCW estimator in terms of efficiency since it solves the efficient influence curve estimating equation. Thus, under appropriate regularity conditions, the A-IPCW estimator is locally asymptotically efficient. However, like the IPCW estimator, the A-IPCW estimator is not a substitution estimator and may also be unstable.

## 20.2 C-TMLEs

The collaboratively double robustness property states that a TMLE  $Q_{n,g_n}^*$  of  $Q_0$  is consistent if the estimator  $g_n$  of  $g_0$  correctly adjusts for the variables that explain the additive residual bias of the initial estimator  $Q_n$  with respect to  $Q_0$ . Thus the collaborative double robustness of TMLE teaches us that consistency of the TMLE does not require that either the estimator of  $Q_0$  or the estimator of  $g_0$  is consistent, but rather, one should be concerned with reducing the distance between,  $Q_{n,g_n}^*$  and  $Q_0$ , and,  $g_n$  and  $g_0$ , such that the resulting estimator  $\Psi(Q_{n,g_n}^*)$  is close to  $\Psi(Q_0)$ . If  $Q_n$  does a very good job estimating  $Q_0$ , very little adjustment is necessary through the estimate of  $g_0$ ; on the other hand, if  $Q_n$  is a poor estimator of  $Q_0$ , the estimator  $g_n$  will have to do a better job of approximating  $g_0$ .

C-TMLE is an extension of TMLE that takes advantage of the collaborative double robustness property of those estimators by constructing  $g_n$  in collaboration with  $Q_n$ . C-TMLE uses the log-likelihood or another loss function for  $Q_0$  to choose from a sequence of  $K$  targeted maximum likelihood estimates  $Q_n^{k*}$  indexed by initial estimates of  $Q_0$  and  $g_0$ . Recall the procedure:

1. Create  $Q_n$ , an initial estimator of  $Q_0$ .
2. Generate a sequence of estimates of  $g_0$ :  $g_n^0, g_n^1, \dots, g_n^{K-1}, g_n^K$ , where  $g_n^0$  is the least data-adaptive estimate and  $g_n^K$  is the most data-adaptive estimate of  $g_0$ .
3. Generate the initial TMLE estimate,  $Q_n^{0*}$ , indexed by  $Q_n$  and  $g_n^0$ .
4. Generate a sequence of TMLE estimates:  $Q_n^{0*}, Q_n^{1*}, \dots, Q_n^{K-1*}, Q_n^{K*}$ , indexed by corresponding estimators  $g_n^0, \dots, g_n^K$ , where each TMLE in this sequence has a larger log-likelihood than the previous TMLE. This monotonicity is ensured by defining the next TMLE as the TMLE that uses the previous TMLE in the sequence as initial estimator, each time the log-likelihood of the TMLE does not increase with the same initial estimator just by virtue of using the more data-adaptive estimate of  $g_0$ .
5. Finally, choose among the sequence of TMLEs using loss-based cross-validation with log-likelihood loss.

One adjustment to the above methodology, discussed in the previous chapter, is to use a penalized loss function when parameters are borderline identifiable. This is an important consideration in observational studies and the issue of choosing an appropriate penalty is addressed in Sect. 20.5.

The C-TMLE has two distinct advantages over the TMLE methodology:

1. C-TMLE may be used to produce stable estimators of borderline identifiable parameters while TMLE may breakdown in these situations (the estimating equation methods discussed above are even more susceptible than TMLE to breaking down). The reason many parameters are not identifiable, or are borderline identifiable, is due to violations of ETA or the more general positivity assumption, where a certain level of a covariate or group of covariates is completely predictive of treatment/exposure/censoring. In these situations, where sparsity of the data with respect to the target parameter is an issue, C-TMLE is able to weight the bias–variance tradeoff of adjusting for certain covariates in estimating these weakly identifiable parameters. C-TMLE only adjusts for covariates in estimating  $g_0$  when they appear to be beneficial to the estimate of the parameter of interest and selects against adjusting for covariates which are detrimental to the estimate of  $\Psi(Q_0)$ , weighing both bias and variance. All other methods that rely on an estimate of  $g_0$  use a loss function that measures the fit of  $g_0$  itself, or a priori specify a parametric model, and thereby ignore the effect adjusting for certain covariates has on the final estimate of the parameter of interest.
2. The C-TMLE is often more efficient in finite samples than the TMLE. In fact, in some rare situations, the C-TMLE is super efficient by having an asymptotic variance smaller than the semiparametric efficiency bound. For example, if the initial estimator  $Q_n$  is an MLE for a correctly specified parametric model. The finite sample and asymptotic super-efficient behavior is a consequence of the collaborative double robustness exploited by the C-TMLE. In situations where the initial estimate  $Q_n$  is a very good estimate of  $Q_0$  in the targeted sense, little adjustment is needed from the estimate of  $g_0$ . The more one adjusts for covariates in the estimator of  $g_0$ , the larger the variance of the final estimator of the parameter of interest. In fact, it can be shown that once the estimator of  $g_0$  adjusts for all covariates that explain the residual bias of the initial estimator as an estimator of  $Q_0$ , then a TMLE update of this latter TMLE will (asymptotically) estimate zero fluctuation. In other words, the theory teaches us that more aggressive efforts for bias reduction are fitting noise! Thus not adjusting much in  $g_n$  when one doesn't have to provides estimators with smaller variance.

The C-TMLE exhibits all of the advantages of the TMLE discussed in previous chapters, as well as these two major advantages. The advantages of the C-TMLE are particularly useful in observational studies, where practical violations of the positivity assumption are a concern. However, in studies where treatment is randomized, C-TMLEs are also appropriate for two distinct reasons. First, informative censoring may be an issue, and practical violations of the ETA assumption may be attributed to this censoring. Second, one may adjust for covariates in the treatment mechanism  $g_0$  in order to gain efficiency since C-TMLEs address the bias–variance tradeoff of adjusting for particular variables. Thus, implementation of the C-TMLE in RCTs will help ensure that one does not adjust in  $g_n$  for the covariates in a way that hinders the estimate of the parameter of interest.

### 20.3 Data, Model, and Parameters of Interest

The time-to-event data structure presented in Sect. 18.1 is the data structure of interest here. However, since we are now interested in observational data, there is an additional arrow from  $W$  to  $A$  in the causal graph. This new data structure suggests the following orthogonal factorization of the likelihood of the observed data structure  $O$  under a probability distribution  $P$ :

$$\mathcal{L}(O | P) = \underbrace{P(W)}_{Q_W} \underbrace{P(A | W)}_{g_A} \prod_{t=1}^K \underbrace{P(dN(t) | \bar{N}(t-1), \bar{A}(t-1), A, W)}_{Q_{dN(t)}} \underbrace{P(dA(t) | \bar{N}(t), \bar{A}(t-1), A, W)}_{g_{A(t)}}.$$

Thus, the likelihood of  $O$  factorizes, just as the general censored data structure presented in Sect. 20.1, into a portion corresponding to the full-data distribution  $Q_0$  and a portion corresponding to the censoring and treatment mechanism  $g_0$ .  $Q_0$  is composed of the baseline covariate distribution  $Q_{W,0}(W)$  and  $\bar{Q}_0(t | A, W) \equiv E_0(dN(t) | \bar{N}(t-1) = 0, \bar{A}(t-1) = 0, A, W)$ , the intensity of the event-counting process given  $A$  and  $W$ , conditioning on “no event yet.” We further factorize  $g_0$  into the treatment mechanism  $g_{A,0}$  and censoring mechanism intensity  $\bar{g}_0(t | A, W) \equiv E_0(dA(t) | \bar{N}(t) = 0, \bar{A}(t-1) = 0, A, W)$ , which is the intensity of the censoring process given  $A$  and  $W$ , conditioning on “no event yet.” Let’s also define  $S_0(t_k | A, W) = P_0(T > t_k | A, W)$ , which is the conditional survival function of the event of interest and can be expressed in terms of the intensity of the event process  $\bar{Q}_0$  under the CAR assumption:

$$S_0(t_k | A, W) = \prod_{t=1}^{t_k} [1 - \bar{Q}_0(t | A, W)].$$

Note that  $\bar{Q}_0(t | A, W)$  is the conditional hazard of  $T$  at  $t$ , given  $A, W$ , under CAR, which holds if  $T$  and  $C$  are conditionally independent, given  $A, W$  (which is implied by our causal graph). The parameters of interest depicted in Sect. 18.3, when  $A$  is randomized, are the same parameters of interest now that we have moved to the observational setting. Moreover, the methods in Sect. 18.5 for estimating the TMLE of these parameters are exactly the same for the observational setting.

### 20.4 Estimators of the Treatment-Specific Survival Function

In this section we will briefly discuss the MLE, IPCW estimator, and A-IPCW estimator for the treatment-specific survival curve. These three methods will then be compared to the TMLE/C-TMLE in a simulation study. MLEs are one class of estimators for estimating the treatment-specific survival function, discussed in

Chap. 18, and we show in Sect. 18.3 how to map  $\bar{Q}_n$  into  $\psi_n^{MLE} = \Psi_a(Q_n)(t_k)$ , the MLE of the treatment-specific survival curve  $\Psi_a(Q_0)(t_k)$  at time  $t_k$ . The IPCW method for estimating the treatment-specific survival curve only relies on an estimator of  $g_0$ . This estimating-equation-based estimator may take the following form:

$$\psi_{n,a}^{IPCW} = \frac{1}{n} \sum_{i=1}^n \frac{I(T_i > t_k)I(C_i > t_k)I(A_i = a)}{g_{n,A}(a|W_i) \prod_{s=1}^{t_k} (1 - \bar{g}_n(s | A_i, W_i))}.$$

The A-IPCW estimator is a double robust estimator that solves the efficient-influence-curve-based estimating equation. Thus, this estimator requires estimates of  $Q_0$  and  $g_0$ . The efficient influence curve for the treatment-specific survival curve at time  $t_k$  for the observed data structure is

$$\begin{aligned} D_a^*(P_0) = & \sum_{t \leq t_k} H_{0,a}^*(t | A, W) \left[ I(\tilde{T} = t, \Delta = 1) - I(\tilde{T} \geq t) \bar{Q}_0(t | A = a, W) \right] \\ & + S_0(t_k | A = 1, W) - \Psi_a(P_0)(t_k), \end{aligned}$$

where

$$H_{0,a}^*(t | A, W) = - \frac{I(A = a)}{g_{A,0}(A = a | W) \prod_{i=1}^{t_k} (1 - \bar{g}_0(i | A, W))} \frac{S_0(t_k | A, W)}{S_0(t | A, W)} I(t \leq t_k).$$

Recall that  $H_{0,a}^*(t | A, W)$  is the time-dependent clever covariate used to define the TMLE of the treatment-specific survival function  $S_{0,a}(t_k) = P_0(T_a > t_k)$ , and, by the  $\delta$ -method, it forms the building block of the time-dependent clever covariate of any desired causal contrast in terms of such treatment-specific survival functions. Hubbard et al. (1999) develop the one-step A-IPCW estimator that solves the efficient influence curve estimating equation. The resulting A-IPCW estimate is given by

$$\begin{aligned} \psi_{n,a}^{A-IPCW} = & \frac{1}{n} \sum_{i=1}^n \sum_{t \leq t_k} H_{n,a}^*(t, A_i, W_i) \left[ I(\tilde{T}_i = t, \Delta_i = 1) \right. \\ & \left. - I(\tilde{T}_i \geq t) \bar{Q}_n(N_1(t) = 1 | A = a, W_i) \right] + S_n(t_k | A = a, W_i), \end{aligned}$$

where  $H_{n,a}^*(t | A, W)$  is  $H_a(t | A, W)$  with estimates  $g_{n,A}$ ,  $\bar{g}_n$ , and  $S_n$  substituted for  $g_{A,0}$ ,  $\bar{g}_0$ , and  $S_0$ . It is important to note that  $\psi_{n,a}^{IPCW}$  and  $\psi_{n,a}^{A-IPCW}$  might not be written as a substitution estimator  $\Psi_a(Q_n)$  for a particular  $Q_n$ .

## 20.5 C-TMLE of the Treatment-Specific Survival Function

There are two requirements for extending the TMLE to a C-TMLE. First, a sequence of estimates of  $g_0$  and corresponding sequence of TMLEs of  $Q_0$  must be generated. Second, the TMLE from that sequence of TMLEs that has the minimum cross-validated risk based on the initial loss function (or a loss function that is

asymptotically equivalent with that loss function) for  $Q_0$  is chosen. Thus, in order to implement the C-TMLE, one must choose a method for sequencing the estimates of  $g_0$ , and a loss function for  $Q_0$  that is asymptotically equivalent to the log-likelihood loss function used by the TMLE.

Since  $g_0$  factorizes into both a treatment mechanism  $g_{A,0}$  and censoring intensity  $\bar{g}_0$ , the sequence of estimates of  $g_0$  must be a sequence of estimates of both the treatment and censoring mechanisms. Therefore, we propose a sequence of estimates where, for each element in the sequence, either the censoring or treatment mechanism is more nonparametric than it was in the previous step. Since main terms that are data-adaptive fits of the covariate profile may be constructed, using main terms regressions for these estimates is reasonable and lends itself nicely to defining a sequence of estimates of  $g_0$ . We describe the process below for main terms, which are simply the observed covariates.

Suppose one observes  $A$ , and  $K$  baseline covariates  $W_1 \dots W_K$ , and  $\tau$  is the last time point observed for any subject. First, an initial estimate  $\bar{Q}_n$  of the conditional hazard  $\bar{Q}_0$  is constructed using super learner based on the log-likelihood loss function. This estimate  $\bar{Q}_n$  is held fixed. Next, we present an iterative algorithm that generates a sequence of  $J$  moves  $M_0, \dots, M_J$ , where  $J = 2 \times K + 1$ . For each move, there is a corresponding TMLE:  $(\bar{Q}_n^{0*}, g_n^0), \dots, (\bar{Q}_n^{J*}, g_n^{J*})$ . Note, that the superscript now denotes the number of moves that index the TMLE. There should be no confusion with the superscript before, which denoted the iteration number since the  $*$  indicates a TMLE that is fully iterated. Each move  $M_j$  corresponds with two main terms regression models: a main terms logistic regression model for  $g_{A,0}$ , and a main terms logistic regression model for  $\bar{g}_0$ .  $M_0$  is the logistic intercept model for  $g_{A,0}$ , and a logistic regression fitting time nonparametrically for  $\bar{g}_0$ :

$$M_0 = \begin{cases} \text{logit}[P(A = 1|W_1, \dots, W_K)] = \beta_0, \\ \text{logit}[P(A(t) = 1|A(t-1) = 0, N(t) = 0, A, W_1, \dots, W_K)] \\ \quad = \alpha_0 + \alpha_1 I(t = 2) + \dots + \alpha_L I(t = L). \end{cases}$$

The next step  $M_1$  in the sequence consists of  $g_{A,M_1}$  and  $\bar{g}_{M_1}$ , which are constructed by adding a main term to either  $g_{A,M_0}$  or  $\bar{g}_{M_0}$ . So the set of possible  $g_{A,M_1}$  is constructed by adding a main term from the set  $\{W_1, \dots, W_K\}$  to  $g_{A,M_0}$  and the set of possible  $\bar{g}_{M_1}$  are constructed by adding a main term from the set  $\{A, W_1, \dots, W_K\}$  to  $\bar{g}_{M_0}$ . The TMLE corresponding with such a candidate estimator of  $g_0$ , and using  $\bar{Q}_n$  as initial estimator of the hazard, is evaluated at each possible  $M_1$ , and the main term that maximizes the increase in the penalized log-likelihood of the TMLE is the next move in the sequence. The estimate for which a main term is not added remains the same as in the previous step in the sequence. The variable that is added is then removed from the possible set of moves in the next step for that particular component of  $g_0$  (i.e., the treatment mechanism or the censoring mechanism). This process is continued until none of the possible steps for augmenting the fit of  $g_0$  increases the penalized log-likelihood of the corresponding TMLE. At this point, the construction of the clever covariate  $H_1$  is complete, and the corresponding TMLE becomes the initial estimator for the next TMLE in the sequence. The TMLE estimate based

on  $M_j$ , where  $j$  is the last completed step in the sequence, becomes the new initial  $\bar{Q}_n$  for the TMLE algorithm and a new clever covariate  $H_2$  is constructed. The estimates of  $g_0$  in  $M_{j+1}$  are now chosen based on adding a main term to the previous fit of  $g_0$  implied by  $M_j$  as before. Thus, given this choice  $M_j$ , the  $g_{A,M_j}$ ,  $\bar{g}_{M_j}$ , and  $j$ th TMLE  $\bar{Q}_n^{j*}$  are used to construct the next TMLE,  $\bar{Q}_n^{(j+1)*}$ , in the sequence. This process is continued until all  $2 \times K + 1$  possible moves are completed, updating the initial estimator of  $\bar{Q}_0$  each time, and building a new clever covariate when necessary. The number of moves completed indexes the different candidate TMLEs, and the optimal number of moves should be chosen by using  $V$ -fold (possibly penalized) log-likelihood-based cross-validation.

Figure 20.1 presents a diagram of the sequencing algorithm for an example data set with two baseline covariates. The top displays how an initial estimate  $\bar{Q}_n$  and the first move  $M_0$ , resulting in two fits  $g_{A,M_0}$  and  $\bar{g}_{M_0}$ , map into the first TMLE of the conditional hazard in the sequence,  $\bar{Q}_n^{0*}$ . Furthermore, that TMLE has a particular penalized log-likelihood fit. In the example, the penalized log-likelihood of  $\bar{Q}_n^{0*}$  associated with  $M_0$  is  $-3,364$ . The remainder of the diagram shows how the moves are constructed by building on  $M_0$ . Each box includes, in the upper left hand corner the main terms that are available to construct the possible moves, in the upper right hand corner the initial estimate of  $\bar{Q}_0$  for that move, and in the bottom right hand corner the possible moves that may be made. In the box for  $M_1$ , the move that maximizes the penalized log-likelihood is the one that adds  $W_2$  to  $g_{A,M_0}$  (penalized log-likelihood of  $-3,349$ ). This move is chosen and added to the list of chosen moves as  $M_1$  and  $\bar{g}_{M_1}$  is set to  $\bar{g}_{M_0}$ . Subsequently, the variable that was chosen is removed from the table of available moves in the next step ( $W_2$  is crossed out in the table of available moves for  $\bar{g}_{M_2}$  in the next box). This process is continued until none of the moves increases the penalized log-likelihood from the preceding step. This occurs at  $M_3$ . Then, the initial estimate of  $\bar{Q}_0$  is set to the previous TMLE in the sequence,  $\bar{Q}_n^{2*}$ , and the process is continued. The rest of sequence of chosen moves is populated in this fashion.

An extension of the above sequencing procedure that uses data-adaptive methods to estimate  $g_0$  is also possible. One may incorporate more data-adaptive techniques by allowing the main terms to be super learning fits of both the treatment and censoring mechanisms based on a growing set of explanatory variables. Furthermore, the suggested sequencing algorithm presented here is one of many possible ways to construct a sequence of increasingly nonparametric estimates of  $g_0$ ; in practice, alternative sequencing methods may be implemented.

Chapter 19 discusses a penalty to robustify the estimation procedure in the context of sparsity, specifically, in situations where the efficient influence curve has large values for good fits of  $g_0$ . The penalty term should make the criterion more targeted toward the parameter of interest while preserving the log-likelihood as the dominant term in situations where identifiability is not in jeopardy, as it is when there is no practical violation of the positivity assumption. Thus, the penalty term should be asymptotically negligible but of importance in a sparse data setting. For this reason we choose an estimator of the variance of the  $\bar{Q}_0$ -component of the efficient influence curve as our penalty, where the  $\bar{Q}_0$ -component is the sum over time



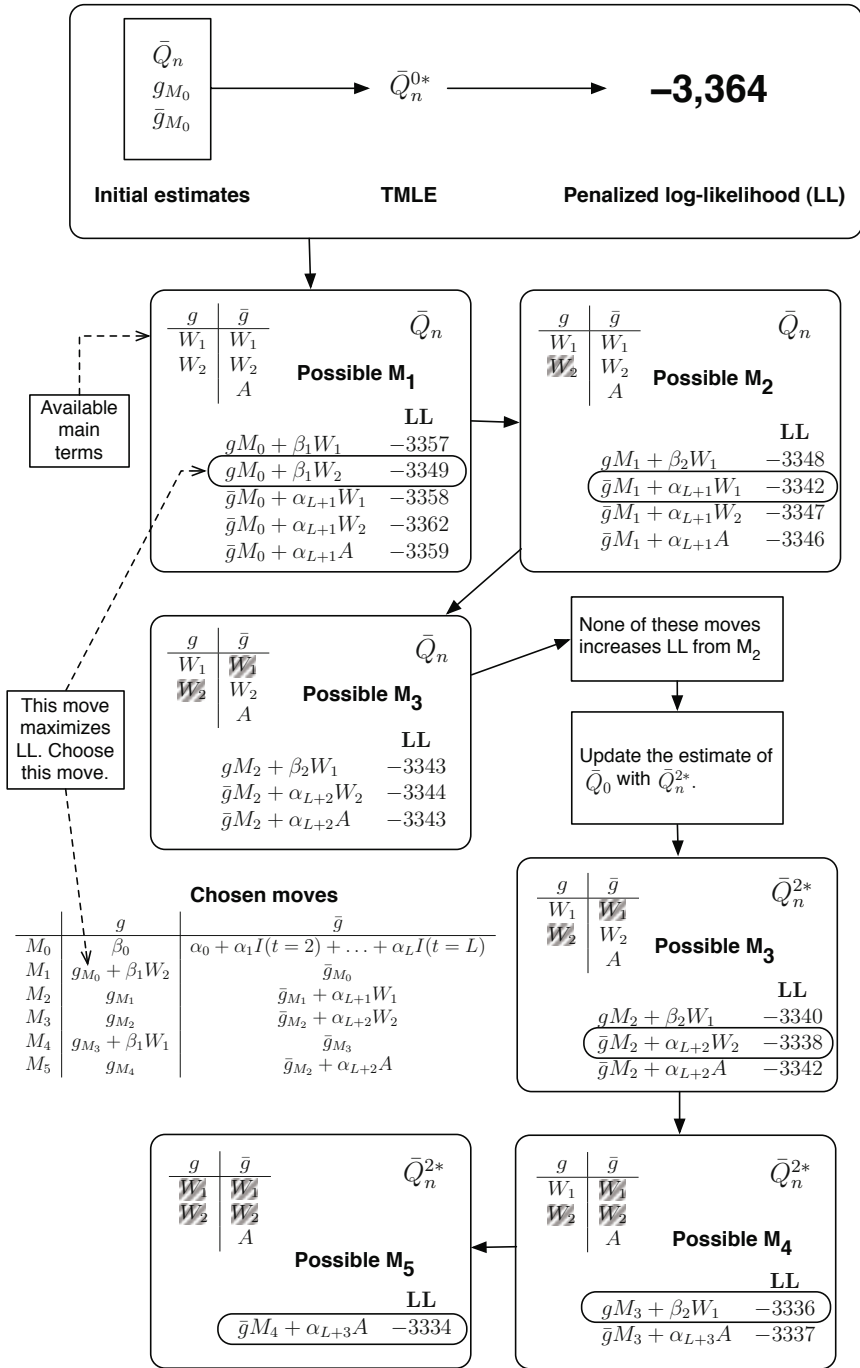


Fig. 20.1 Example of sequencing algorithm for data set with two baseline covariates

of the the time-specific clever covariate multiplied by the counting process residual. The variance of the efficient influence curve is asymptotically negligible relative to the log-likelihood, and in situations where there is a violation of the positivity assumption, as in the case when  $g_{n,A}$  or  $\prod_{i=1}^t (1 - \bar{g}_n(i | A, W))$  is very close to zero for a given subject, it will severely penalize the log-likelihood. Using a standard method for estimating the variance of a martingale, we obtain the following variance term:

$$\frac{1}{n} \sum_i^n \sum_t^{t_k} \frac{1}{g_{n,A}(a | W) \prod_{i=1}^t (1 - \bar{g}_n(i | a, W))} \frac{S_n(t_k | a, W)}{S_n(t | a, W)} I(t \leq t_k) \bar{Q}_n(1 - \bar{Q}_n)(t | a, W).$$

This penalty becomes large when the probability  $A = a$  is small, even for values of  $W$  for which  $A = a$  is not observed in the data. Thus, this penalty is sensitive to lack of identifiability, including theoretical nonidentifiability.

Now that a sequence of fits of  $g_0$  and a penalized loss function for  $\bar{Q}_0$  have been defined, the C-TMLE algorithm can be implemented:

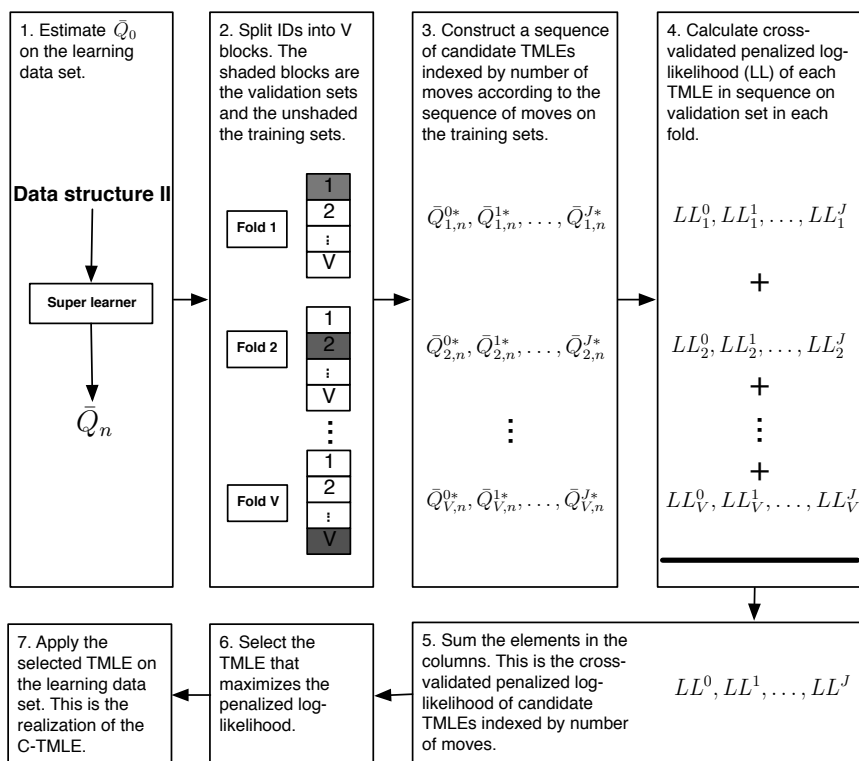
1. Estimate  $Q_{W,0}$  with the empirical probability distribution.
2. Generate  $\bar{Q}_n$ , an estimate of the discrete failure time hazard  $\bar{Q}_0$ , using super learner based on the log-likelihood loss function (step 1 in Fig. 20.2).
3. Use  $V$ -fold cross-validation with the log-likelihood loss function penalized by the variance term above to choose among the TMLE algorithms indexed by the number of moves (steps 2–6 in Fig. 20.2).
4. Implement the sequencing algorithm on the full data set for the chosen number of moves.
5. The resulting  $\bar{Q}_n^*$  from the TMLE indexed by the chosen number of moves is the C-TMLE of the conditional hazard.
6. Construct the substitution estimator  $\Psi(Q_n^*)$  with  $Q_n^* = (Q_{W,n}, \bar{Q}_n^*)$ , which is the C-TMLE of the parameter of interest.

Several variations of this sequencing algorithm and penalized likelihood can also be explored to see if they produce more robust estimators in sparse data situations.

**Trimming.** Observations that led to identifiability problems are removed from fitting  $g_0$ . This is done in order to obtain estimates that are not as influenced by outlying values in  $W$  and were highly predictive of treatment/censoring.

**Truncation.** Observations that led to identifiability problems are set to a minimum probability. All subjects who have a treatment mechanism that predicted treatment less than  $p\%$  of the time, where  $p$  is small, are set to  $p\%$ .

**Using binary covariates.** Transform the continuous variables into binary variables that are indicators of the quantiles of the original variable. This allows the C-TMLE algorithm to adjust for only the regions that do not cause positivity violations, as opposed to the entire variable. Thus, the larger the number of binary variables constructed from an initial covariate, the more flexibility the C-TMLE algorithm has. However, too many binary variables for a single continuous covariate may contribute to loss of signal and a large increase in the computation time of the algorithm.



**Fig. 20.2** Cross-validation using penalized log-likelihood to choose among a sequence of TMLEs

Using binary covariates had the largest positive effect on producing robust estimates in our simulations, and trimming and truncation had little effect on the results in the simulations presented below. Furthermore, a dimension-reduction step in between the initial fit of  $\bar{Q}_0$  and the C-TMLE sequencing step improved computation time tremendously. This was done by removing all variables from the sequencing step that fell below a certain cutoff in terms of association with the outcome of interest after accounting for the initial fit. Univariate regression was performed with the initial estimate as an offset and all variables that fell below a 0.10-FDR-adjusted  $p$ -value were no longer considered in the sequencing step. All C-TMLEs presented in the remainder of this chapter include the dimension-reduction step, and use binary covariates for the secondary sequencing step.

C-TMLEs and corresponding estimates  $g_n$  solve the efficient influence curve equation, just like the TMLE. This provides the basis for the generally applicable asymptotic linearity theorem for C-TMLE as presented in Chap. 19 and Appendix A. Thus, confidence intervals may be constructed for C-TMLE in the same way as they are constructed for TMLE in Chap. 18.

## 20.6 Simulations

The simulations consist of data sets generated under three scenarios: no ETA violation, medium ETA violation, and high ETA violation. Within each scenario, estimates are presented for each of the methods using a correct parametric model for the conditional hazard and a purposely misspecified parametric model. The simulated data were generated as follows:

1. Baseline covariates  $W = \{W_1, W_2, W_3, W_4, W_5\}$  were generated from a multivariate normal with mean 0, variance 1, and covariance 0.2. If any  $W$  was greater than 2 or less than  $-2$ , it was set to 2 or  $-2$ , respectively, to ensure that the treatment and censoring mechanisms were appropriately bounded.
2. Treatment  $A$  was generated as a binomial:

$$P_0(A = 1 \mid W) = \text{expit}(0.4 + 0.4W_1 + 0.4W_2 - 0.5W_3 + \log(\text{ETA}_{OR}) \times W_4),$$

where  $\text{ETA}_{OR}$  is the odds ratio implied by the coefficient of  $W_4$ , and  $W_4$  is the baseline covariate responsible for violations in the ETA assumption in the simulated data sets.  $\text{ETA}_{OR}$  equals 1 for the scenario under no ETA violation, 10 for medium ETA violation, and 15 for high ETA violation.

3. The event process was generated using the following hazard at each  $t$ :

$$P_0(T = t \mid T \geq t, A, W) = \text{expit}(0.25 - 0.6W_1 - 0.6W_2 - 0.6W_3 - A).$$

4. The censoring process was generated using the following hazard at each  $t$ :

$$P_0(C = t \mid C \geq t, A, W) = \text{expit}(-3 - 0.1W_1 - 0.1W_2 - 0.1W_3 - 0.1A).$$

Under each level of ETA violation, 500 data sets of 500 observations were generated. The following estimators were used to estimate the parameter of interest, which is the treatment-specific survival curve for  $A = 1$  at time 2: IPCW estimator  $\psi_{n,1}^{IPCW}(2)$ , MLE  $\psi_{n,1}^{MLE}(2)$ , A-IPCW estimator  $\psi_{n,1}^{A-IPCW}(2)$ , TMLE  $\psi_{n,1}^{TMLE}(2)$ , A-IPCW estimator without  $W_4$ , TMLE without  $W_4$ , and C-TMLE  $\psi_{n,1}^{C-TMLE}(2)$  as described in Sect. 20.5 with dimension reduction, penalized log-likelihood loss function, and binary baseline covariates split at the 33rd and 66th percentile. Each of these methods was implemented twice for each data set: once using the correct parametric model for  $\bar{Q}_0$  and once using a purposely misspecified parametric model for  $\bar{Q}_0$  that only included  $A$  and  $W_5$  as main terms in the logistic hazard regression. Note that  $W_5$  is just a noise variable and does not play a role in the outcome process, censoring process, or treatment mechanism. For estimators requiring an estimate of  $g_{A,0}$  and  $\bar{g}_0$ , they were estimated based on the correctly specified parametric model.

The A-IPCW estimator without  $W_4$  and TMLE without  $W_4$  are not estimators one could implement based on a real data set, but were evaluated to compare the C-TMLE algorithm to methods where the irrelevant variable causing identifiability problems was known and removed. Furthermore, all of the estimation methods except for C-TMLE were given the true parametric model for  $g_0$ , an advantage they

would not have when analyzing real data. In a real data analysis, model selection that uses a loss function for fitting the treatment and censoring mechanisms would be implemented.

The problem variable may be a confounder in some scenarios. In order to evaluate the methods under this situation, we reran the high ETA violation scenario with a minor change. The treatment was generated as a binomial as  $P_0(A = 1 \times W) = \text{expit}(0.4 + \log(15) \times W_1 + 0.4W_2 - 0.5W_3)$ . Instead of varying the odds ratio for  $W_4$ , we set the odds ratio for  $W_1$ , one of the variables that affects the hazard of the event of interest, to 15.

### 20.6.1 Results: Point Estimates

Tables 20.1–20.3 display the simulation results where the variable causing identifiability concerns is not a confounder. The true value of the parameter being estimated is 0.462. Table 20.1 shows that all estimators of the parameter of interest are unbiased when the initial model for  $\bar{Q}_0$  is specified correctly ( $Q_C$ ). However, when the initial model for  $\bar{Q}_0$  is misspecified ( $Q_M$ ), the MLE is biased. The IPCW estimate is the same for the misspecified and correctly specified model for  $\bar{Q}_0$  since this estimate does not depend on an estimate of the conditional hazard of  $T$ .

The fact that all of the methods produce unbiased estimators of the parameter of interest, even for the moderate sample sizes examined here, suggests that bias should not be the standard by which these estimators are judged. Assessing the methods in terms of MSE begins to distinguish the methods from one another. Table 20.2 presents the root mean square error, relative efficiency (on the variance scale), and the efficiency bound for each scenario. Again, in the no ETA scenario, all estimators have essentially the same MSE. However, as the ETA becomes larger, some of the methods begin to demonstrate their advantages while others lose all stability.

1. The IPCW estimator is highly unstable with increasing ETA. In fact, the C-TMLE is six times more efficient when the conditional failure time hazard  $\bar{Q}_0$  is estimated consistently and almost 3.5 times more efficient when  $\bar{Q}_0$  is misspecified with medium ETA. For the high ETA case, the C-TMLE is 15.5 times more efficient for a consistently estimated  $\bar{Q}_0$  and eight times more efficient when the parametric model for  $\bar{Q}_0$  is misspecified. The C-TMLE is 3.5 more times efficient than the A-IPCW estimator for a consistently estimated  $\bar{Q}_0$ , and 2.6 times more efficient for a misspecified parametric model for  $\bar{Q}_0$  with medium ETA. For high ETA, the C-TMLE is 6.5 and 4.5 times more efficient for the respective ways of estimating  $\bar{Q}_0$ .
2. The TMLE, regardless of ETA, tends to have an MSE that approaches the efficiency bound, unlike the IPCW or A-IPCW estimator.
3. The C-TMLE shows super efficient behavior, and even as the ETA violation increases, the MSE remains close to the level it was under no ETA violation. This is true whether  $\bar{Q}_0$  is fit well or misspecified. The MSE is lower when  $\bar{Q}_0$  is es-

**Table 20.1** Mean estimates ( $\psi_0 = 0.462$ ); variable causing violation in ETA is not a confounder

Method	No ETA		Medium ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$	$Q_C$	$Q_M$
TMLE	0.460	0.460	0.463	0.460	0.465	0.458
MLE	0.461	0.473	0.461	0.499	0.461	0.501
IPCW	0.460	0.460	0.461	0.461	0.460	0.460
A-IPCW	0.460	0.460	0.463	0.464	0.464	0.466
A-IPCW w/o $W_4$	0.460	0.460	0.460	0.455	0.460	0.455
TMLE w/o $W_4$	0.460	0.460	0.460	0.455	0.460	0.455
C-TMLE	0.460	0.463	0.460	0.460	0.461	0.463

**Table 20.2** RMSE and relative efficiency; variable causing violation in ETA is not a confounder

Method	No ETA		Medium ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$	$Q_C$	$Q_M$
Efficiency bound	0.028		0.046		0.060	
<i>RMSE</i>						
TMLE	0.029	0.029	0.051	0.056	0.062	0.065
MLE	0.027	0.030	0.028	0.047	0.028	0.049
IPCW	0.029	0.029	0.071	0.071	0.106	0.106
A-IPCW	0.029	0.029	0.054	0.061	0.070	0.081
A-IPCW w/o $W_4$	0.029	0.029	0.030	0.031	0.029	0.031
TMLE w/o $W_4$	0.029	0.029	0.030	0.031	0.029	0.030
C-TMLE	0.028	0.031	0.029	0.037	0.029	0.040
<i>Relative efficiency</i>						
TMLE	1.0	1.1	1.2	1.5	1.0	1.2
MLE	0.9	1.1	0.4	1.0	0.2	0.7
IPCW	1.0	1.0	2.4	2.4	3.1	3.1
A-IPCW	1.0	1.1	1.4	1.8	1.3	1.8
A-IPCW w/o $W_4$	1.0	1.1	0.4	0.5	0.2	0.3
TMLE w/o $W_4$	1.0	1.1	0.4	0.4	0.2	0.3
C-TMLE	1.0	1.2	0.4	0.7	0.2	0.4

**Table 20.3** Characteristics of C-TMLE; variable causing violation in ETA is not a confounder

Method	No ETA		Medium ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$	$Q_C$	$Q_M$
Mean # of moves	0.1	13.4	0.1	10.5	0.1	10.1
<i>% of time C-TMLE algorithm chose:</i>						
Zero Moves	0.98	0.00	0.98	0.06	0.99	0.08
$W_1$	0.00	0.99	0.00	0.93	0.00	0.89
$W_2$	0.00	0.99	0.00	0.91	0.00	0.89
$W_3$	0.00	0.99	0.00	0.81	0.00	0.81
$W_4$ (ETA Variable)	0.01	0.84	0.00	0.47	0.00	0.41
$W_5$	0.01	0.00	0.01	0.00	0.01	0.00

timated consistently; however, it still outperforms any of the other estimators in terms of efficiency when the parametric model for  $\bar{Q}_0$  is misspecified.

Of note, for high ETA, the A-IPCW estimates range from 17.5 to 103%, the estimates generated by the TMLE range from 30.3 to 63.8%, and the C-TMLE produces estimates ranging from 35.6 to 59.2%. Thus, it becomes immediately clear that the A-IPCW estimator does not respect the global constraints of the model by producing an estimate that is not a probability (one of the estimates is greater than 100%). In addition, the A-IPCW estimator is an empirical mean of an unbounded function of the data; thus when the estimates of  $g_0$  are close to zero, the contribution from one observation may be too large or even infinite. On the other hand, the estimates generated by TMLE and C-TMLE are empirical means of probabilities. Since they are substitution estimators, each observation's contribution is bounded and may be no larger than 1. The advantage of substitution estimators is directly observed in the simulation results by the smaller RMSE for TMLE than A-IPCW.

Table 20.3 presents characteristics of the C-TMLE algorithm. When  $\bar{Q}_0$  is consistently estimated, the C-TMLE algorithm makes very few moves and, in almost all cases, it makes zero moves relying on the intercept models for  $g_0$ . However, when  $\bar{Q}_0$  is misspecified, the C-TMLE algorithm selects more moves and attempts to adjust in the estimator of  $g_0$  for the variables that were not adjusted for in the initial estimate of  $\bar{Q}_0$ . Also, the algorithm resists choosing the region of the variable that causes the ETA violations illustrated by the fact that  $W_4$  is selected fewer times as ETA increases.

Tables 20.4–20.6 display the results where confounder  $W_1$  is also the variable causing identifiability problems. The “No ETA” columns are the same as in the previous tables. As before, when  $\bar{Q}_0$  is consistently estimated, all of the estimators are unbiased. However, when the parametric model for  $\bar{Q}_0$  is misspecified, the TMLE, IPCW estimator, and A-IPCW estimator remain unbiased, the MLE is highly biased, and the C-TMLE is slightly biased. The bias in the C-TMLE is due to the fact that it is not fully adjusting for  $W_1$  when regions of that variable contribute to nonidentifiability of the parameter of interest. This bias is compensated for by the small variance, as the C-TMLE does as well as any of the other methods in terms of RMSE. Furthermore, the A-IPCW estimator fails to achieve the efficiency bound and performs twice as poorly as the C-TMLE in terms of RMSE, as seen in Table 20.5. Though the IPCW estimator behaved reasonably in terms of bias and MSE, its potential to generate highly unstable estimates was displayed in the previous simulations.

Table 20.6 displays the characteristics of the C-TMLE algorithm. Again, when  $\bar{Q}_0$  is consistently estimated, very few moves are made, and when it is misspecified, the algorithm adjusts by choosing a fuller model for  $g_0$ . As expected, the C-TMLE algorithm has a difficult time choosing what variables to adjust for now that the ETA variable is a confounder. This can be seen by the fact that the algorithm continues to adjust for  $W_1$  more often than it did for  $W_4$  in Table 20.3. The algorithm uses the penalized loss function to weight whether it is better to adjust for a variable that is associated with the outcome or remove it since it causes identifiability problems. In this case, the algorithm has chosen to adjust for at least some region of the variable

**Table 20.4** Mean estimates ( $\psi_0 = 0.462$ ); variable causing violation in ETA is a confounder

Method	No ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$
TMLE	0.460	0.460	0.468	0.459
MLE	0.461	0.473	0.462	0.552
IPCW	0.460	0.460	0.461	0.461
A-IPCW	0.460	0.460	0.462	0.466
A-IPCW w/o $W_1$	0.460	0.460	0.462	0.533
TMLE w/o $W_1$	0.460	0.460	0.462	0.533
C-TMLE	0.460	0.463	0.462	0.482

**Table 20.5** RMSE and relative efficiency; variable causing violation in ETA is a confounder

Method	No ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$
Efficiency bound	0.028		0.054	
<i>RMSE</i>				
TMLE	0.029	0.029	0.053	0.050
MLE	0.027	0.030	0.029	0.094
IPCW	0.029	0.029	0.058	0.058
A-IPCW	0.029	0.029	0.052	0.077
A-IPCW w/o $W_1$	0.029	0.029	0.032	0.076
TMLE w/o $W_1$	0.029	0.029	0.031	0.076
C-TMLE	0.028	0.031	0.031	0.055
<i>Relative efficiency</i>				
TMLE	1.0	1.1	1.0	0.9
MLE	0.9	1.1	0.3	3.0
IPCW	1.0	1.0	1.2	1.2
A-IPCW	1.0	1.1	0.9	2.0
AIPW w/o $W_1$	1.0	1.1	0.3	2.0
TMLE w/o $W_1$	1.0	1.1	0.3	2.0
C-TMLE	1.0	1.2	0.3	1.1

**Table 20.6** Characteristics of C-TMLE; variable causing violation in ETA is a confounder

Method	No ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$
Mean # of moves	0.103	13.389	0.134	8.448
<i>% of time C-TMLE algorithm chose:</i>				
Zero Moves	0.98	0.00	0.97	0.12
$W_1$ (ETA Variable)	0.00	0.99	0.00	0.88
$W_2$	0.00	0.99	0.00	0.80
$W_3$	0.00	0.99	0.00	0.59
$W_4$	0.01	0.84	0.01	0.48
$W_5$	0.01	0.00	0.02	0.00



a large percentage of the time. Had the algorithm decided to remove the variable completely from the adjustments, the estimator would have been more biased, and the RMSE would be very large, like those seen for the TMLE without  $W_1$  estimator. This difference in RMSE illustrates the value of generating binary variables for the C-TMLE.

## 20.6.2 Results: Inference

Table 20.7 presents the coverage probabilities where the ETA variable is not a confounder. Ideally, a well-behaved method would produce confidence intervals that include the truth 95% of the time. Since each scenario was only simulated 500 times, some variation from 95% is not unexpected. (The confidence intervals for the MLE are not reported as that would require an application of a  $\delta$ -method to compute the correct influence curve based on the assumed parametric model, and no theory is available when MLE is based on a machine learning algorithm.) The A-IPCW estimator is the only method that has 95% confidence intervals over all scenarios (excluding the estimator that doesn't adjust for the ETA variable since that estimator is not feasible in a real data setting). The influence-curve-based confidence intervals for the TMLE begin to deteriorate with increasing ETA. The C-TMLE coverage probability also decreases with increasing ETA but not as quickly as for the TMLE, and only when  $Q_0$  is misspecified. Table 20.8 displays the 95% coverage probabilities when the ETA variable is a confounder. Again, the TMLE and C-TMLE coverage probabilities are less than 95% when  $Q_0$  is misspecified. Thus, we can conclude that the theoretically valid asymptotic influence-curve-based confidence intervals are not producing proper coverage in finite samples when lack of identifiability is an issue. Furthermore, as the parameter becomes more nonidentifiable, the coverage probabilities further deteriorate.

Tables 20.7 and 20.8 also present the mean width of the influence-curve-based confidence intervals for each estimator. While the A-IPCW estimator provides confidence intervals with proper coverage, the width of these intervals are larger than the intervals of both the TMLE and C-TMLE. In fact, in Table 20.7, the average A-IPCW confidence-interval width for high ETA with inconsistent initial estimator of  $Q_0$  is almost twice as large as the C-TMLE interval width. When the ETA variable is a confounder, under high ETA and misspecified  $Q_0$ , the A-IPCW intervals are 67% larger on average than the C-TMLE intervals.

Although the A-IPCW intervals include the truth 95% of the time, in many cases they are extremely large, rendering these estimates useless. The data sets where A-IPCW estimates have large intervals are not the ones where TMLE/C-TMLE have difficulty with coverage. In fact, for high ETA, the TMLE/C-TMLE influence-curve-based confidence intervals include the truth for almost all data sets where the AIPW estimate is below 0.35 or above 0.60. The TMLE/C-TMLE intervals that do not include the truth are very close to including it. This suggests that a small adjustment

**Table 20.7** Coverage probabilities and mean width of confidence intervals; variable causing violation in ETA is not a confounder

Method	No ETA		Medium ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$	$Q_C$	$Q_M$
<i>Coverage probabilities</i>						
TMLE	0.94	0.96	0.86	0.85	0.80	0.83
IPCW	0.98	0.98	0.92	0.92	0.88	0.88
A-IPCW	0.94	0.95	0.95	0.95	0.94	0.94
A-IPCW w/o $W_4$	0.94	0.95	0.95	0.96	0.95	0.96
TMLE w/o $W_4$	0.94	0.96	0.96	0.95	0.95	0.96
C-TMLE	0.94	0.94	0.95	0.92	0.94	0.89
<i>Mean width of confidence intervals</i>						
TMLE	0.11	0.12	0.19	0.21	0.21	0.24
IPCW	0.14	0.14	0.24	0.24	0.27	0.27
A-IPCW	0.11	0.12	0.18	0.22	0.20	0.25
A-IPCW w/o $W_4$	0.11	0.12	0.11	0.12	0.11	0.12
TMLE w/o $W_4$	0.11	0.12	0.11	0.12	0.11	0.12
C-TMLE	0.11	0.12	0.11	0.13	0.11	0.13

**Table 20.8** Coverage probabilities and mean width of confidence intervals; variable causing violation in ETA is a confounder

Method	No ETA		High ETA	
	$Q_C$	$Q_M$	$Q_C$	$Q_M$
<i>Coverage probabilities</i>				
TMLE	0.94	0.96	0.87	0.93
IPCW	0.98	0.98	0.94	0.94
A-IPCW	0.94	0.95	0.94	0.92
A-IPCW w/o $W_1$	0.94	0.95	0.94	0.38
TMLE w/o $W_1$	0.94	0.96	0.94	0.38
C-TMLE	0.94	0.94	0.94	0.82
<i>Mean width of confidence intervals</i>				
TMLE	0.11	0.12	0.18	0.20
IPCW	0.14	0.14	0.21	0.21
A-IPCW	0.11	0.12	0.17	0.25
A-IPCW w/o $W_1$	0.11	0.12	0.12	0.12
TMLE w/o $W_1$	0.11	0.12	0.12	0.12
C-TMLE	0.11	0.12	0.11	0.15

to the TMLE/C-TMLE influence-curve-based confidence intervals would cause the TMLE/C-TMLE intervals to include the truth.

For high ETA, the A-IPCW confidence intervals tend to be larger than the TMLE confidence intervals in the region of standard errors that produce useful confidence intervals; however, in the region where the confidence intervals are not useful, the reverse is true. The average length of the A-IPCW confidence interval is 0.255 compared to 0.237 for the TMLE and 0.132 for the C-TMLE. Even though the A-IPCW estimator produces confidence intervals with proper coverage, they are larger than

the TMLE intervals and almost twice as large as the C-TMLE intervals, which have only slightly less coverage. The standard errors are almost always larger for the A-IPCW estimator vs. the C-TMLE for this simulation. In fact, none of the standard errors for C-TMLE exceeds 0.1, while 5.4% of the A-IPCW standard errors exceed 0.15. Thus, the difference in coverage probabilities (0.94 vs. 0.89) is compensated for by the fact that a large percent of A-IPCW confidence intervals are too large to be practically useful.

**Adjustment for targeted methods.** The TMLE and C-TMLE confidence intervals would include the truth if the intervals were slightly shifted to the left or the right. We hypothesize that this departure from normality is the result of a distribution of estimates that is slightly skewed in finite samples. This suggests that bootstrap methods, which use the 0.025 and 0.975 bootstrap quantiles to construct confidence intervals, would produce valid 95% confidence intervals. In order to test this hypothesis, 500 additional data sets were generated according to the original simulation high ETA scenario and bootstrap confidence intervals, both based on quantiles and estimated standard error, as well as influence-curve-based confidence intervals were compared for the TMLE. We note this was not done for the C-TMLE due to the prohibitive amount of time it would take to run the bootstrap for 500 data sets; however, for one data set it is a feasible method for inference, and the bootstrap results for the TMLE intervals should hold for C-TMLE. These results are presented in [Table 20.9](#). The resulting coverage probability was 94% using quantile-based-bootstrap intervals, compared to 88% for bootstrap intervals based on the estimated standard error, and 87% using influence-curve-based confidence intervals. Furthermore, the average length of the confidence intervals was 0.21, 0.22, and 0.26, respectively. This suggests that the quantile-based bootstrap, which naturally accounts for the skewness in finite samples, is able to produce valid 95% confidence intervals. The lack of coverage for the standard-error-based bootstrap confidence intervals confirms that the skewness of the distribution of the estimates in finite samples contributes to the poor influence curve based confidence intervals. This is due to the fact that both of these methods depend on the standard normal quantiles to generate confidence intervals. Not only do the quantile-based bootstrap confidence intervals produce the proper coverage, but they also are 20% smaller than the influence-curve-based intervals. Thus, the quantile-based bootstrap intervals should be the preferred method for constructing TMLE and C-TMLE confidence intervals in the presence of sparsity.

**Table 20.9** Bootstrap vs. influence-curve-based 95% confidence intervals for TMLE

	Coverage probabilities	Mean CI width
Quantile bootstrap	0.94	0.21
Wald bootstrap	0.88	0.22
Wald influence curve	0.87	0.26

## 20.7 Discussion

Ultimately, a choice must be made to implement an estimator that behaves the best across the largest number of possible scenarios. The simulations presented here illustrate the advantages of the C-TMLE methodology for estimating causal parameters when analyzing time-to-event outcomes. The results show that the C-TMLE does at least as well as the best estimator under every scenario and, in many of the more realistic scenarios, behaves much better than the next best estimator in terms of both bias and variance. Unlike other estimators that rely on an external estimator of nuisance parameters, the C-TMLE algorithm estimates the nuisance parameters with consideration for the parameter of interest. The C-TMLE is an entirely a priori specified method that accounts for the fact that there are identifiability concerns in observational data and addresses these issues uniformly, rather than handling them on a case-by-case basis, or ignoring them completely. The C-TMLE algorithm accomplishes this by using a targeted (penalized) loss function to make smart choices in determining what variables to adjust for in the estimate of  $g_0$  and only adjusts for variables that have not been fully adjusted for in the initial estimate of  $Q_0$ . This allows the C-TMLE estimates to exhibit super efficiency and behave almost as well as the MLE when the model for  $Q$  is specified correctly. In addition, when the initial estimator of  $Q_0$  is not specified correctly, the C-TMLE adjusts in the secondary step only for the variables that improve the estimate of the parameter of interest by considering the bias–variance tradeoff for each adjustment. These decisions are always made with respect to how they affect the estimate of the parameter of interest and are not dependent on a loss function designed for the prediction of the treatment/censoring mechanism itself, as it is in the other methods presented. By ignoring the effect of each adjustment on the estimate of the parameter of interest, the other methods have been shown to be highly unstable in finite samples. Furthermore, the TMLE and C-TMLE are substitution estimators and obey the proper bounds of the true model contributing to their overall stability. Lastly, the bootstrap provides a method to construct valid 95% confidence intervals for the C-TMLE that are tighter than the intervals produced by other methods when estimating weakly identifiable parameters.