Chapter 4
Introduction to TMLE

Sherri Rose, Mark J. van der Laan

This is the second chapter in our text to deal with estimation. We started by defining the research question. This included our data, model for the probability distribution that generated the data, and the target parameter of the probability distribution of the data. We then presented the estimation of prediction functions using super learning. This leads us to the estimation of causal effects using the TMLE. This chapter introduces TMLE, and a deeper understanding of this methodology is provided in Chap. 5. Note that we use the abbreviation *TMLE* for *targeted maximum likelihood estimation* and the *targeted maximum likelihood estimator*. Later in this text, we discuss *targeted minimum loss-based estimation*, which can also be abbreviated *TMLE*.

For the sake of demonstration, we have considered the data structure $O = (W, A, Y) \sim P_0$. Our statistical model for the probability distribution P_0 is nonparametric. The target parameter for this example is $E_{W,0}[E_0(Y \mid A = 1, W) - E_0(Y \mid A = 0, W)]$, which can be interpreted as a causal effect under nontestable assumptions formalized by an SCM, including the randomization assumption and the positivity assumption. In Chap. 3, we estimated $E_0(Y \mid A, W)$ using super learning. With super learning we are able to respect that the statistical model does not allow us to assume a particular parametric form for the prediction function $E_0(Y \mid A, W)$. We could have estimated the entire conditional density of the outcome Y, but then we would be estimating portions of the density we do not need. In particular, this would mean that our initial estimator, such as a super learner of this conditional density of Y, would be targeted toward the complete conditional density, even though it is better to target it toward the conditional mean of Y. Estimating only the relevant portion of the density of O in this first step of the TMLE procedure provides us with a maximally efficient (precise) and unbiased procedure: the practical and asymptotic performance of the TMLE of ψ_0 only cares about how well $\bar{Q}_0$ is estimated.

The super learner fit can be plugged into the target parameter mapping to obtain a corresponding estimator of the target parameter. In other words, for each subject in the sample, one would evaluate the difference between the predicted value of Y under treatment ($A = 1$) and control ($A = 0$) and average these differences across all subjects in the sample.

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However, this super learner maximum likelihood (ML)-based substitution estimator is not targeted toward the parameter of interest. The super learner prediction function was tailored to optimally fit the overall prediction function $E_0(Y \mid A, W)$, spreading its errors uniformly to (successfully) optimize average squared prediction errors, and thereby suffers from a nonoptimal bias–variance tradeoff for the causal effect of interest. Specifically, this ML-based super learner of the causal effect will be biased.

Our TMLE procedure improves on the ML-based substitution estimator by reducing bias for the target parameter of interest. The initial super learner fit for $E_0(Y \mid A, W)$ is the first step in the TMLE procedure. The second stage of the TMLE procedure is a step targeted toward modifying the initial estimator of $E_0(Y \mid A, W)$ in order to make it less biased for the target parameter. That is, the second stage of TMLE is tailored to get the best estimate of our target parameter of interest, with respect to bias and variance, instead of a best estimate of the overall prediction function $E_0(Y \mid A, W)$. We cover the entire TMLE procedure in this chapter, assuming the reader has knowledge based on the material presented in Chap. 3.

We explain the TMLE procedure in multiple ways in these two chapters, with the goal of reinforcing the method and targeting different levels of understanding (conceptual, applied, theoretical). Thus, the applied researcher may only be interested in a thorough understanding of the conceptual and applied sections, whereas the more theoretically inclined mathematician may wish to also read the technical derivations and Appendix A.

TMLE Methodology Summary

TMLE is a two-step procedure where one first obtains an estimate of the data-generating distribution P_0, or the relevant portion Q_0 of P_0. The second stage updates this initial fit in a step targeted toward making an optimal bias–variance tradeoff for the parameter of interest $\Psi(Q_0)$, instead of the overall density P_0. The procedure is double robust and can incorporate data-adaptive likelihood-based estimation procedures to estimate Q_0 and the treatment mechanism. The double robustness of TMLE has important implications in both randomized controlled trials and observational studies, with potential reductions in bias and gains in efficiency.

We use our mortality study example to present an application of TMLE. As a reminder, in this study we are interested in the effect of LTPA on death. We have binary Y, death within 5 years of baseline, and binary A indicating whether the subject meets recommended levels of physical activity. The data structure in this example is $O = (W, A, Y) \sim P_0$. While we use this basic data structure and a particular target parameter to illustrate the procedure, TMLE is a very flexible general method for estimating any particular target parameter of a true probability distribution that is known to be an element of any particular statistical model. We will demonstrate its implementation with a variety of specific data structures throughout this text. In Appendix A, we also present a general TMLE of causal effects of

multiple time point interventions for complex longitudinal data structures. However, we find introducing TMLE in the context of a simple data structure is helpful for many people. Starting with Appendix A is often overwhelming, and that appendix is geared toward those who desire a comprehensive and rigorous statistical understanding or wish to develop TMLE for unique applications encountered in practice, corresponding with a choice of data structure, statistical model, and target parameter, not previously addressed.

TMLE has many attractive properties that make it preferable to other existing estimators of a target parameter of the probability distribution of the data. We fully detail these properties in Chaps. 5 and 6, after introducing them in this chapter, and compare other estimators to TMLE based on these properties. Of note, TMLE removes all the asymptotic residual bias of the initial estimator for the target parameter, if it uses a consistent estimator of the treatment mechanism. If the initial estimator was already consistent for the target parameter, the slight additional fitting of the data in the targeted step will potentially remove some finite sample bias, and certainly preserve this consistency property of the initial estimator.

As a consequence, the TMLE is a so-called double robust estimator. In addition, if the initial estimator and the estimator of the treatment mechanism are both consistent, then it is also asymptotically efficient according to semiparametric statistical model efficiency theory. It allows the incorporation of machine learning (i.e., super learning) methods for the estimation of both $\bar{Q}_0$ and g_0 so that we do not make assumptions about the probability distribution P_0 we do not believe. In this manner, every effort is made to achieve minimal bias and the asymptotic semiparametric efficiency bound for the variance.

TMLE is also a substitution estimator. Substitution estimators are plug-in estimators, taking an estimator of the relevant part of the data-generating distribution and plugging it into the mapping $\Psi()$. Substitution estimators respect the statistical model space (i.e., the global constraints of the statistical model) and respect that the target parameter ψ_0 is a number obtained by applying the target parameter mapping Ψ to a particular probability distribution in the statistical model. Substitution estimators are therefore more robust to outliers and sparsity than nonsubstitution estimators.

4.1 Motivation

Let us step back for a moment and discuss why we are here. We want to estimate a parameter $\Psi(P_0)$ under a semiparametric statistical model that represents actual knowledge. Thus we don't want to use a misspecified parametric statistical model that makes assumptions we know to be false. We also know that an ML-based substitution estimator is not targeted to the parameter we care about. While we like this approach as it is flexible, it is still not a targeted approach. TMLE is a *targeted* substitution estimator that incorporates super learning to get the best estimate of our

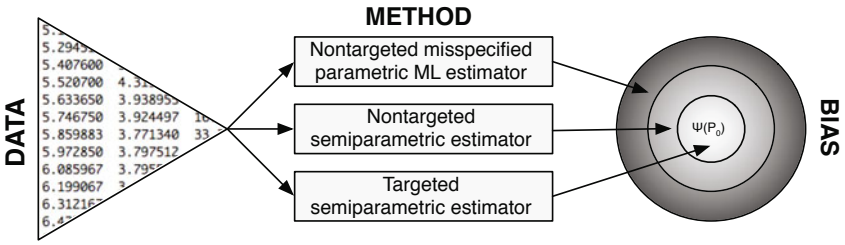

Fig. 4.1 Illustration of bias for different methods

target parameter; it is tailored to be a minimally biased method while also being tailored to fully utilize all the information in the data.

We illustrate this in Fig. 4.1. The outermost ring is furthest from the truth, and that represents the estimate we achieve using a misspecified parametric statistical model. The middle ring in our target improves on the misspecified parametric statistical model, but it still does not contain the truth. This ring is our nontargeted semiparametric statistical model approach (super learning). The innermost circle contains the true $\Psi(P_0)$, and this is what we have the potential to achieve with super learning *and* TMLE combined. We refer to the combined two-stage approach as TMLE, even though it is understood that the initial estimator and estimator of the treatment mechanism should be based on super learning respecting the actual knowledge about P_0.

4.2 TMLE in Action: Mortality Study Example

In Chap. 3, we discussed the implementation of super learning for our simplified mortality study example. In this section we analyze the actual data, updating the super learner estimate of $\bar{Q}_0$ with a targeting step. This section serves as an introduction to the implementation of TMLE in a concrete example: the data structure is $O = (W, A, Y) \sim P_0$, the nonparametric statistical model is augmented with causal assumptions, and the targeted parameter is $\Psi(P_0) = E_{W,0}[E_0(Y \mid A = 1, W) - E_0(Y \mid A = 0, W)]$, which represents the causal risk difference under these causal assumptions. The mean over the covariate vector W in $\Psi(P_0)$ is simply estimated with the empirical mean, so that our substitution TMLE will be of the type

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

where $Q_n = (\bar{Q}_n, Q_{W,n})$ and $Q_{W,n}$ is the empirical distribution for the marginal distribution of W. The second step in the TMLE will update our initial estimate of $\bar{Q}_0$. We will use the superscript 0 to denote this initial estimate, in conjunction with the

Table 4.1 SPPARCS variables

Variable	Description
Y	Death occurring within 5 years of baseline
A	LTPA score $\geq$ 22.5 METs at baseline[‡]
W_1	Health self-rated as "excellent"
W_2	Health self-rated as "fair"
W_3	Health self-rated as "poor"
W_4	Current smoker
W_5	Former smoker
W_6	Cardiac event prior to baseline
W_7	Chronic health condition at baseline
W_8	$x \leq 60$ years old
W_9	$60 < x \leq 70$ years old
W_{10}	$80 < x \leq 90$ years old
W_{11}	$x > 90$ years old
W_{12}	Female

[‡] LTPA is calculated from answers to a detailed questionnaire where prior performed vigorous physical activities are assigned standardized intensity values in metabolic equivalents (METs). The recommended level of energy expenditure for the elderly is 22.5 METs.

subscript n thus we have $\bar{Q}_n^0$ as our initial estimate of $\bar{Q}_0$. Information from the treatment mechanism (or exposure mechanism; we use these terms interchangeably) is used to update $\bar{Q}_n^0$ and target it toward the parameter of interest. In this example, our treatment mechanism is $g_0 = P_0(A \mid W)$. Our updated estimate of $\bar{Q}_0$ is denoted $\bar{Q}_n^1$.

Data. The National Institute of Aging-funded Study of Physical Performance and Age-Related Changes in Sonomans (SPPARCS) is a population-based, census-sampled, study of the epidemiology of aging and health. Participants of this longitudinal cohort were recruited if they were aged 54 years and over and were residents of Sonoma, CA or surrounding areas. Study recruitment of 2092 persons occurred between May 1993 and December 1994 and follow-up continued for approx. 10 years. The data structure is $O = (W, A, Y)$, where $Y = I(T \leq 5 \text{ years})$, T is time to the event death, A is a binary categorization of LTPA, and W are potential confounders. These variables are further defined in Table 4.1. Of note is the lack of any right censoring in this cohort. The outcome (death within or at 5 years after baseline interview) and date of death was recorded for each subject. Our parameter of interest is the causal risk difference, the average treatment effect of LTPA on mortality 5 years after baseline interview. The cohort was reduced to a size of $n = 2066$, as 26 subjects were missing LTPA values or self-rated health score (1.2% missing data).

4.2.1 Estimator

Estimating $\bar{Q}_0$. In Chap. 3, we generated a super learner prediction function. This is the first step in our TMLE procedure. Thus, we take as inputs our super learner

Table 4.2 Collection of algorithms

Algorithm	Description
glm	Linear model
bayesglm	Bayesian linear model
polymars	Polynomial spline regression
randomForest	Random forest
glmnet,$\alpha = 0.25$	Elastic net
glmnet,$\alpha = 0.50$	
glmnet,$\alpha = 0.75$	
glmnet,$\alpha = 1.00$	
gam, degree = 2	Generalized additive models
gam, degree = 3	
gam, degree = 4	
gam, degree = 5	
nnet,size = 2	Neural network
nnet, size = 4	
gbm, interaction depth=1	Gradient boosting
gbm, interaction depth=2	

prediction function, the initial estimate $\bar{Q}_n^0$, and our data matrix. The data matrix includes columns for each of the covariates W found in Table 4.1, exposure LTPA (A), and outcome Y indicating death within 5 years of baseline. This is step 1 as described in Fig. 4.2. We implemented super learner in the R programming language (R Development Core Team 2010), using the 16 algorithms listed in Table 4.2, recalling that algorithms of the same class with different tuning parameters are considered individual algorithms. Then we calculated predicted values for each of the 2066 observations in our data set, using their observed value of A, and added this as an n-dimensional column labeled $\bar{Q}_n^0(A_i, W_i)$ in our data matrix. Then we calculated a predicted value for each observation where we set $a = 1$, and also $a = 0$, forming two additional columns $\bar{Q}_n^0(1, W_i)$ and $\bar{Q}_n^0(0, W_i)$. Note that for those observations with an observed value of $A_i = 1$, the value in column $\bar{Q}_n^0(A_i, W_i)$ will be equal to the value in column $\bar{Q}_n^0(1, W_i)$. For those with observed $A_i = 0$, the value in column $\bar{Q}_n^0(A_i, W_i)$ will be equal to the value in column in $\bar{Q}_n^0(0, W_i)$. This is depicted in step 2 of Fig. 4.2. At this stage we could plug our estimates $\bar{Q}_n^0(1, W_i)$ and $\bar{Q}_n^0(0, W_i)$ for each subject into our substitution estimator of the risk difference:

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

This is the super learner ML-based substitution estimator discussed previously, plugging in the empirical distribution $Q_{W,n}^0$ for the marginal distribution of W, and the super learner $\bar{Q}_n^0$ for the true regression $\bar{Q}_0$. We know that this estimator is not targeted towards the parameter of interest, so we continue on to a targeting step.

Estimating g_0. Our targeting step required an estimate of the conditional distribution of LTPA given covariates W. This estimate of $P_0(A \mid W) \equiv g_0$ is denoted g_n and was obtained using super learning and the same algorithms listed in Table 4.2. We estimated predicted values using this new super learner prediction function, adding two more columns to our data matrix: $g_n(1 \mid W_i)$ and $g_n(0 \mid W_i)$. This can be seen in Fig. 4.2 as step 3.

Determining a parametric working model to fluctuate the initial estimator. The targeting step used the estimate g_n in a clever covariate to define a parametric working model coding fluctuations of the initial estimator. This clever covariate $H_n^*(A, W)$ is given by

$$H_n^*(A, W) \equiv \left(\frac{I(A = 1)}{g_n(1 \mid W)} - \frac{I(A = 0)}{g_n(0 \mid W)} \right).$$

Thus, for each subject with $A_i = 1$ in the observed data, we calculated the clever covariate as $H_n^*(1, W_i) = 1/g_n(1 \mid W_i)$. Similarly, for each subject with $A_i = 0$ in the observed data, we calculated the clever covariate as $H_n^*(0, W_i) = -1/g_n(0 \mid W_i)$. We combined these values to form a single column $H_n^*(A_i, W_i)$ in the data matrix. We also added two columns $H_n^*(1, W_i)$ and $H_n^*(0, W_i)$. The values for these columns were generated by setting $a = 0$ and $a = 1$. This is step 4 in Fig. 4.2.

Updating $\bar{Q}_n^0$. We then ran a logistic regression of our outcome Y on the clever covariate using as intercept the offset $\text{logit}\bar{Q}_n^0(A, W)$ to obtain the estimate ϵ_n, where ϵ_n is the resulting coefficient in front of the clever covariate $H_n^*(A, W)$. We next wanted to update the estimate $\bar{Q}_n^0$ into a new estimate $\bar{Q}_n^1$ of the true regression function $\bar{Q}_0$:

$$\text{logit}\, \bar{Q}_n^1(A, W) = \text{logit}\, \bar{Q}_n^0(A, W) + \epsilon_n H_n^*(A, W).$$

This parametric working model incorporated information from g_n, through $H_n^*(A, W)$, into an updated regression. One can now repeat this updating step by running a logisitic regression of outcome Y on the clever covariate $H_n^*(A, W)$ using as intercept the offset $\text{logit}\, \bar{Q}_n^1(A, W)$ to obtain the next update $\bar{Q}_n^2$. However, it follows that this time the coefficient in front of the clever covariate will be equal to zero, so that subsequent steps do not result in further updates. Convergence of the TMLE algorithm was achieved in one step. The TMLE of Q_0 was given by $Q_n^* = (\bar{Q}_n^1, Q_{W,n}^0)$. With ϵ_n, we were ready to update our prediction function at $a = 1$ and $a = 0$ according to the logistic regression working model. We calculated

$$\text{logit}\, \bar{Q}_n^1(1, W) = \text{logit}\bar{Q}_n^0(1, W) + \epsilon_n H_n^*(1, W),$$

for all subjects, and then

$$\text{logit}\, \bar{Q}_n^1(0, W) = \text{logit}\bar{Q}_n^0(0, W) + \epsilon_n H_n^*(0, W)$$

for all subjects and added a column for $\bar{Q}_n^1(1, W_i)$ and $\bar{Q}_n^1(0, W_i)$ to the data matrix. Updating $\bar{Q}_n^0$ is also illustrated in step 5 of Fig. 4.2.

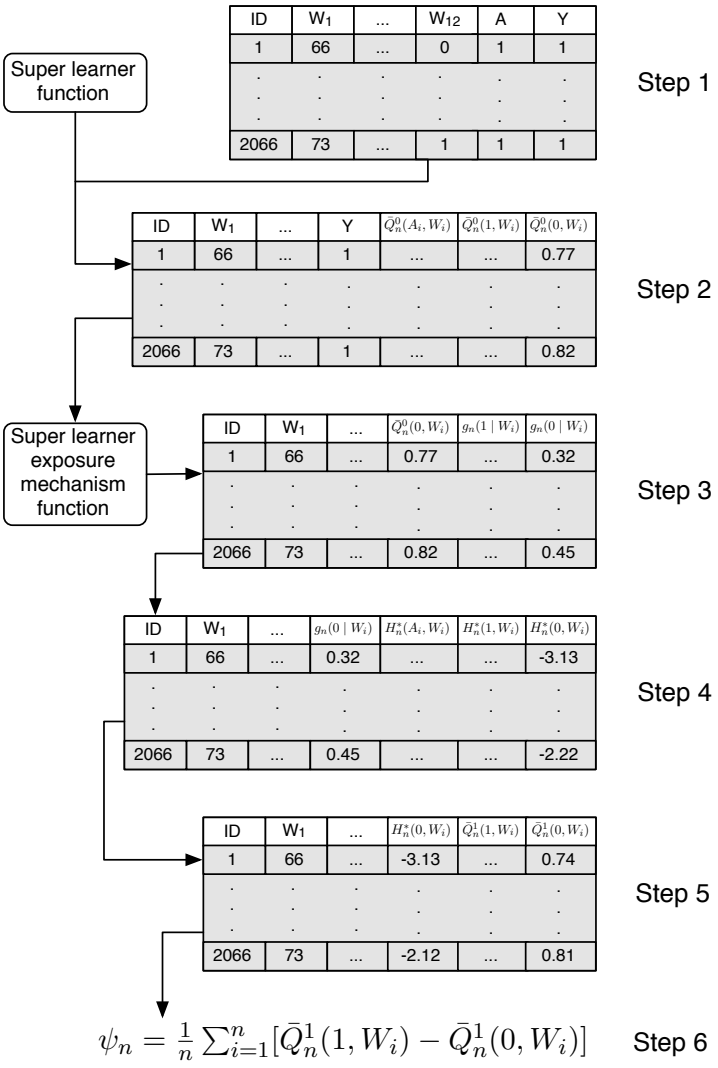

Fig. 4.2 Flow diagram for TMLE of the risk difference in the mortality study example

Targeted substitution estimator of the target parameter. We are at the last step! We computed the plug-in targeted maximum likelihood substitution estimator using the updated estimates $\bar{Q}_n^1(1, W)$ and $\bar{Q}_n^1(0, W)$ and the empirical distribution of W, as seen in step 6 of Fig. 4.2. Our formula from the first step becomes

$$\psi_{TMLE,n} = \Psi(Q_n^*) = \frac{1}{n}\sum_{i=1}^{n}\{\bar{Q}_n^1(1, W_i) - \bar{Q}_n^1(0, W_i)\}.$$

This mapping was accomplished by evaluating $\bar{Q}_n^1(1, W_i)$ and $\bar{Q}_n^1(0, W_i)$ for each observation i, and plugging these values into the above equation. Our estimate of the causal risk difference for the mortality study was $\psi_{TMLE,n} = -0.055$.

4.2.2 Inference

Standard errors. We then needed to calculate the influence curve for our estimator in order to obtain standard errors:

$$IC_n(O_i) = \left(\frac{I(A_i = 1)}{g_n(1 \mid W_i)} - \frac{I(A_i = 0)}{g_n(0 \mid W_i)}\right)(Y - \bar{Q}_n^1(A_i, W_i)) + \bar{Q}_n^1(1, W_i) - \bar{Q}_n^1(0, W_i) - \psi_{TMLE,n},$$

where I is an indicator function: it equals 1 when the logical statement it evaluates, e.g., $A_i = 1$, is true. Note that this influence curve is evaluated for each of the n observations O_i. The beauty of the influence curve of an estimator is that one can now proceed with statistical inference as if the estimator minus its estimand equals the empirical mean of the influence curve. Next, we calculated the sample mean of these estimated influence curve values: $\bar{IC}_n = \frac{1}{n}\sum_{i=1}^n IC_n(o_i)$, where we use o_i to stress that this mean is calculated with our observed realizations of the random variable O_i. For the TMLE we have $\bar{IC}_n = 0$. Using this mean, we calculated the sample variance of the estimated influence curve values:

$$S^2(IC_n) = \frac{1}{n}\sum_{i=1}^n \left(IC_n(o_i) - \bar{IC}_n\right)^2.$$

Lastly, we used our sample variance to estimate the standard error of our estimator:

$$\sigma_n = \sqrt{\frac{S^2(IC_n)}{n}}.$$

This estimate of the standard error in the mortality study was $\sigma_n = 0.012$.

Confidence intervals and p-values. With the standard errors, we can now calculate confidence intervals and p-values in the same manner you may have learned in other statistics texts. A 95% Wald-type confidence interval can be constructed as:

$$\psi_{TMLE,n} \pm z_{0.975}\frac{\sigma_n}{\sqrt{n}},$$

where z_α denotes the α-quantile of the standard normal density $N(0, 1)$. A p-value for $\psi_{TMLE,n}$ can be calculated as:

$$2\left[1 - \Phi\left(\left|\frac{\psi_{TMLE,n}}{\sigma_n/\sqrt{n}}\right|\right)\right],$$

where Φ denotes the standard normal cumulative distribution function. The p-value was < 0.001 and the confidence interval was $[-0.078, -0.033]$.

Interpretation

The interpretation of our estimate $\psi_{TMLE,n} = -0.055$, under causal assumptions, is that meeting or exceeding recommended levels of LTPA decreases 5-year mortality in an elderly population by 5.5%. This result was significant, with a p-value of < 0.001 and a confidence interval of $[-0.078, -0.033]$.

4.3 Practical Implications

The double robustness and semiparametric efficiency of the TMLE for estimating a target parameter of the true probability distribution of the data has important implications for both the analysis of RCTs and observational studies.

4.3.1 Randomized Controlled Trials

In 2010, a panel of the National Academy of Sciences made a recommendation to the FDA regarding the use of statistical methods for dealing with missing data in RCTs. The panel represented the split in the literature, namely, those supporting maximum-likelihood-based estimation, and specifically the use of multiple imputation (MI) methods, and the supporters of (augmented) inverse probability of censoring weighted (A-IPCW) estimators based on solving estimating equations. As a consequence, the committee's report ended up recommending both methods: a split decision.

Both camps at the table have been right in their criticism. The MI camp has been stating that the IPCW methods are too unstable and cannot be trusted in finite samples as demonstrated in various simulation studies, even though these methods can be made double robust. The A-IPCW camp has expressed that one cannot use methods that rely on parametric models that may cause severe bias in the resulting estimators of the treatment effect.

TMLE provides the solution to this problem of having to choose between two methods that have complementary properties: TMLE is a maximum-likelihood-based method and thus inherits all the attractive properties of maximum-likelihood-based substitution estimators, while it is still double robust and asymptotically efficient. TMLE has all the good properties of both the MI and the A-IPCW estimators, but it does not have the bad properties such as reliance on misspecified parametric models of the maximum-likelihood-based estimation the instability of the IPCW estimators due to not being substitution estimator. The FDA has also repeatedly ex-

pressed a desire for methods that can be communicated to medical researchers. As with maximum-likelihood-based estimation, the TMLE is easier to communicate: it is hard to communicate estimators that are defined as a solution of an estimating equation instead of a maximizer of a well-defined criterion.

TMLE can also be completely aligned with the highly populated maximum-likelihood-based estimation camp: TMLE can use maximum-likelihood-based estimation as the initial estimator, but it will carry out the additional targeting step. Of course, we recommend using the super learner (i.e., machine learning) as the initial estimator, but in an RCT in which one assumes that missingness is noninformative, the use of the parametric maximum likelihood estimation as initial estimator will not obstruct unbiased estimation of the causal effect of interest.

Consider an RCT in which we observe on each unit $(W, A, \Delta, \Delta Y)$, where Δ is an indicator of the clinical outcome being observed. Suppose we wish to estimate the additive causal effect $E_0Y_1 - E_0Y_0$, which is identified by the estimand $E_0[\bar{Q}_0(0, W) - \bar{Q}_0(1, W)]$, where $\bar{Q}_0(A, W) = E_0(Y \mid A, W, \Delta = 1)$ under causal assumptions, including that no unmeasured predictors of Y predict the missingness indicator. The TMLE of this additive causal effect only involves a minor modification of the TMLE presented above, and is derived in Appendix A. That is, the clever covariate is modified by multiplying it by $1/P_0(\Delta = 1 \mid A, W)$, and all outcome regressions are based on the complete observations only.

In an RCT the treatment assignment process, $g_0(1 \mid W) = P_0(A = 1 \mid W)$, is known (e.g., 0.5), and it is often assumed that missingness of outcomes is noninformative, also called missing completely at random. When this assumption holds, the g_n, comprising both the treatment assignment and the censoring or missingness mechanism, is always correctly estimated. Specifically, one can consistently estimate the missingness mechanism $P_0(\Delta = 1 \mid A, W)$ with the empirical proportions for the different treatment groups, thus ignoring the value of W. The TMLE will provide valid type I error control and confidence intervals for the causal effect of the investigated treatment, even if the initial regression estimator $\bar{Q}_n^0$ is completely misspecified.

The use of TMLE also often results in efficiency and bias gains with respect to the unadjusted or other ad hoc estimators commonly employed in the analysis of RCT data. For example, consider the additive causal effect example discussed in this chapter. The unadjusted estimator is restricted to considering only complete cases, ignoring observations where the outcome is missing, and ignoring any covariate information. In this particular example, the efficiency and bias gain is already apparent from the fact that the targeted maximum likelihood approach averages an estimate of an individual effect $\bar{Q}_0(1, W) - \bar{Q}_0(0, W)$ over all observations in the sample, including the observations that had a missing outcome.

TMLE can exploit information in measured baseline and time-dependent covariates, even when there is no missingness or right censoring. This allows for bias reduction due to empirical confounding, i.e., it will adjust for empirical imbalances in the treatment and control arm, and thereby improve finite sample precision (efficiency). To get an insight into the potential gains of TMLE relative to the current standard, we note that the relative efficiency of the TMLE relative to the unadjusted

estimator of the causal additive risk in a standard RCT with two arms and randomization probability equal to 0.5, and no missingness or censoring, is given by 1 minus the R squared of the regression of the clinical outcome Y on the baseline covariates W implied by the targeted maximum likelihood fit of the regression of Y on the binary treatment and baseline covariates. That is, if the baseline covariates are predictive, one will gain efficiency, and one can predict the amount of improvement from the actual regression fit.

Perhaps more importantly, the TMLE naturally adjusts for dropout (missingness) as well and can also be used to assess the effect of treatment under noncompliance, i.e., it is unbiased when standard methods are biased. Unlike an unadjusted estimator that ignores covariate information, TMLE does not rely on an assumption of noninformative missingness or dropout, but allows that missingness and dropout depend on the observed covariates, including time-dependent covariates.

In RCTs, including sequentially randomized controlled trials, one can still fully respect the likelihood of the data and obtain fully efficient and unbiased estimators, without taking the risk of bias due to statistical model misspecification (which has been the sole reason for the application of inefficient unadjusted estimators). On the contrary, the better one fits the true functions Q_0 and g_0, as can be evaluated with the cross-validated log-likelihood, the more bias reduction and efficiency gain will have been achieved.

Prespecification of the TMLE in the statistical analysis plan allows for appropriate adjustment with measured confounders while avoiding the possible introduction of bias should that decision be based on human intervention. Therefore, TMLEs can be used for both the efficacy as well as the safety analysis in Phase II, III, and IV clinical trials. In addition, just like for unadjusted estimators, permutation distributions can be used to obtain finite sample inference and more robust inference.

4.3.2 Observational Studies

At many levels of society one builds large electronic databases that keep track of large patient populations. One wishes to use these dynamic databases to assess safety signals of drugs, evaluate the effectiveness of different interventions, and so on. Comparative effectiveness research concerns the research involved to make such comparisons. These comparisons often involve observational studies, so that one cannot assume that the treatment was randomly assigned. In such studies, standard off-the-shelf methods are biased due to confounding as well as informative missingness, censoring, and possibly biased sampling.

In observational studies, the utilization of efficient and maximally unbiased estimators is thus extremely important. One cannot analyze the effect of high dose of a drug on heart attack in a postmarket safety analysis using logistic regression in a parametric statistical model or Cox proportional hazards models, and put much trust in a p-value. It is already a priori known that these statistical models are misspecified and that the effect estimate will be biased, so under the null hypothesis of no

treatment effect, the resulting test statistic will reject the null hypothesis incorrectly with probability tending to 1 as sample size increases. For example, if the high dose is preferentially assigned to sicker people, then the unadjusted estimator is biased high, a maximum likelihood estimator according to a misspecified parametric model will still be biased high by its inability to let the data speak and thereby adjust for the measured confounders.

As a consequence, the only alternative is to use semiparametric statistical models that acknowledge what is known and what is not known, and use robust and efficient substitution estimators. Given such infinite-dimensional semiparametric statistical models, we need to employ machine learning, and, in fact, as theory suggests, we should not be married to one particular machine learning algorithm but let the data speak by using super learning. That is, one cannot foresee what kind of algorithm should be used, but one should build a rich library of approaches, and use cross-validation to combine these estimators into an improved estimator that adapts the choice to the truth. In addition, and again as theory teaches us, we have to target the fit toward the parameter of interest, to remove bias for the target parameter, and to improve the statistical inference based on the central limit theorem. TMLE combined with super learning provides such a robust and semiparametric efficient substitution estimator, while we maintain the log-likelihood or other appropriate loss function as the principal criterion.

4.4 Summary

TMLE is a general algorithm where we start with an initial estimator of P_0, or a relevant parameter Q_0 of P_0. We then create a parametric statistical model with parameter ϵ through this given initial estimator whose score at $\epsilon = 0$ spans the efficient influence curve of the parameter of interest at the given initial estimator. It estimates ϵ with maximum likelihood estimation in this parametric statistical model and finally updates the new estimator as the corresponding fluctuation of the given initial estimator. The algorithm can be iterated until convergence, although in many common cases it converges in one step.

4.5 Road Map for Targeted Learning

We have now completed the road map for targeted learning depicted in Fig. 4.3. This chapter covered effect estimation using super learner and TMLE, as well as inference. In many cases, we may be interested in a ranked list of effect measures, often referred to as variable importance measures (VIMs). We provided an additional road map (Fig. 4.4) for research questions involving VIMs, which are common in medicine, genomics, and many other fields. We address questions of variable importance in Chaps. 22 and 23.

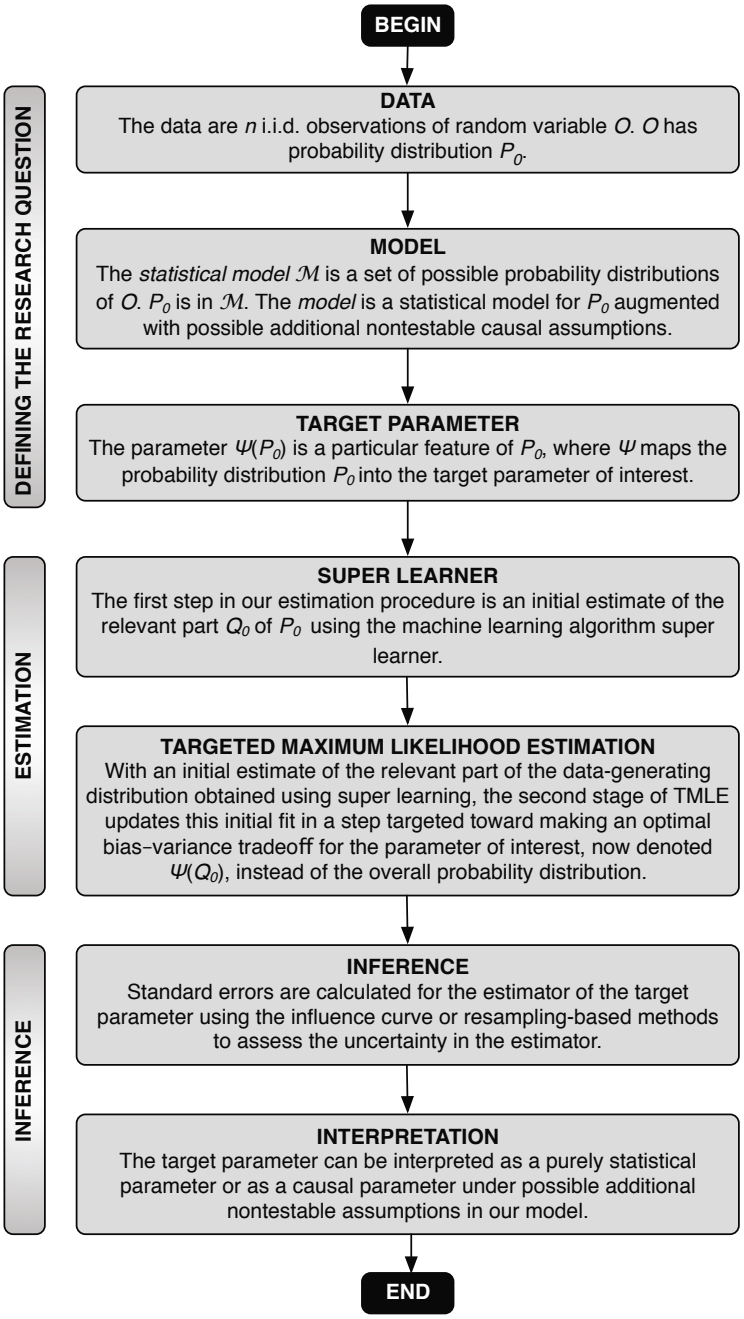

Fig. 4.3 Road map for targeted learning

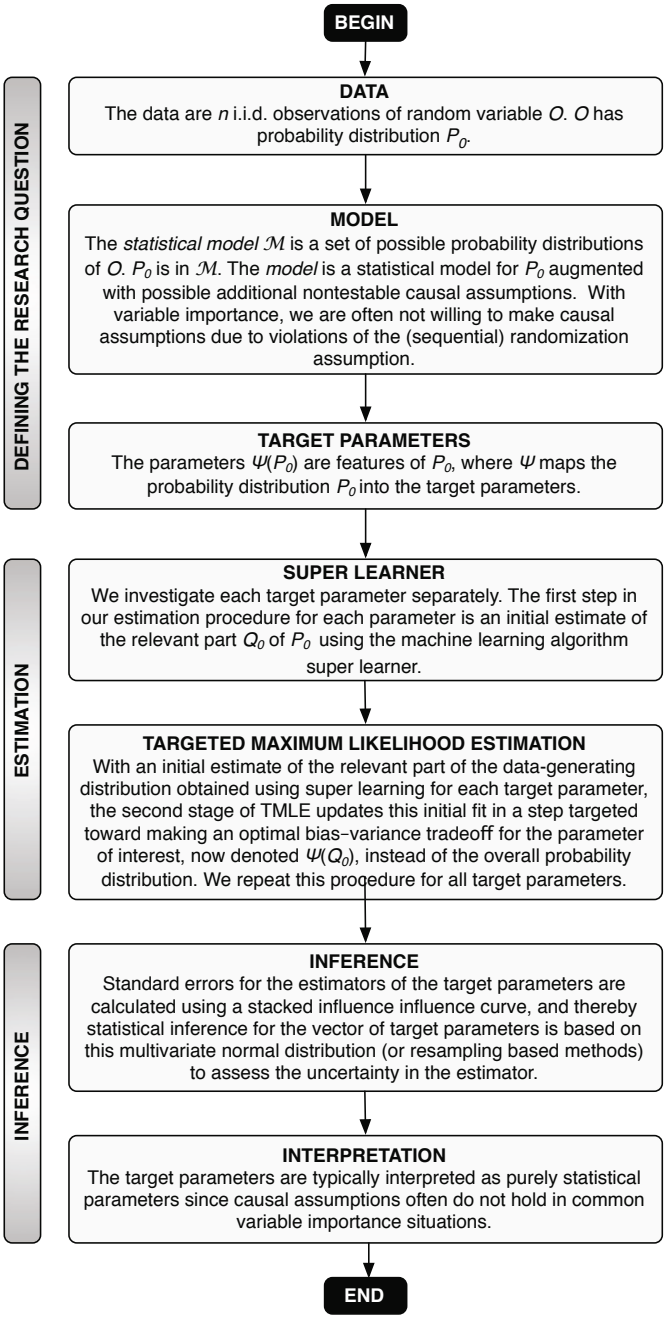

Fig. 4.4 Road map for targeted learning of variable importance measures

4.6 Notes and Further Reading

MLE has been referred to elsewhere as g-formula and g-computation. It is a maximum-likelihood-based substitution estimator of the g-formula parameter. The g-formula for identifying the distribution of counterfactuals from the observed data distribution, under the sequential randomization assumption, was originally published in Robins (1986). We also refer readers to an introductory implementation of a maximum-likelihood-based substitution estimator of the g-formula (Snowden et al. 2011; Rose et al. 2011).

Estimating equation methodology, including IPTW (Robins 1999b; Hernan et al. 2000) and A-IPTW (Robins et al. 2000b; Robins 2000; Robins and Rotnitzky 2001), is discussed in detail in van der Laan and Robins (2003). Detailed references and a bibliographic history on locally efficient A-IPTW estimators, double robustness, and estimating equation methodology can be found in Chap. 1 of that text. A key seminal paper in this literature is Robins and Rotnitzky (1992). A-IPTW was previously referred to as the double robust estimator in some publications. Didactic presentations of IPTW can be found in Robins et al. (2000a), Mortimer et al. (2005), and Cole and Hernan (2008).

For the original paper on TMLE we refer readers to van der Laan and Rubin (2006). Subsequent papers on TMLE in observational and experimental studies include Bembom and van der Laan (2007a), van der Laan (2008a), Rose and van der Laan (2008, 2009, 2011), Moore and van der Laan (2009a,b,c), Bembom et al. (2009), Polley and van der Laan (2009), Rosenblum et al. (2009), van der Laan and Gruber (2010), Gruber and van der Laan (2010a), Rosenblum and van der Laan (2010a), and Wang et al. (2010).

A detailed discussion of multiple hypothesis testing and inference for variable importance measures is presented in Dudoit and van der Laan (2008). We also refer readers to Chaps. 22 and 23. The mortality study analyzed in this chapter with TMLE is based on data discussed in Tager et al. (1998).

Previous work related to estimators in RCTs (and in general in observational studies with known probabilities of treatment) that are robust to model misspecification include, for example, Robins (1994), Robins et al. (1995), Scharfstein et al. (1999), van der Laan and Robins (2003), Leon et al. (2003), Tan (2006), Tsiatis (2006), Moore and van der Laan (2009b), Zhang et al. (2008), Rubin and van der Laan (2008), Freedman (2008a,b), and Rosenblum and van der Laan (2009a).

We refer readers to Bickel et al. (1997) for a text on semiparametric estimation and asymptotic theory. Tsiatis (2006) is a text applying semiparametric theory to missing data, including chapters on Hilbert spaces and influence curves. We also refer to Hampel et al. (1986) for a text on robust statistics, including presentation of influence curves. Van der Vaart (1998) provides a thorough introduction to asymptotic statistics, and van der Vaart and Wellner (1996) discuss stochastic convergence, empirical process theory, and weak convergence theory.