# Chapter 4
# Introduction to TMLE

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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 $\psi_0$ 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 $\psi_0$ is a number obtained by applying the target parameter mapping $\Psi$ 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

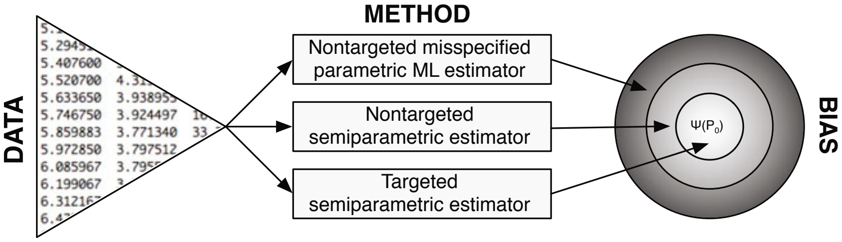


**Fig. 4.1** Illustration of bias for different methods

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 logit$\bar{Q}_n^0(A, W)$ to obtain the estimate $\epsilon_n$, where $\epsilon_n$ 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 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 $\epsilon_n$, 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.

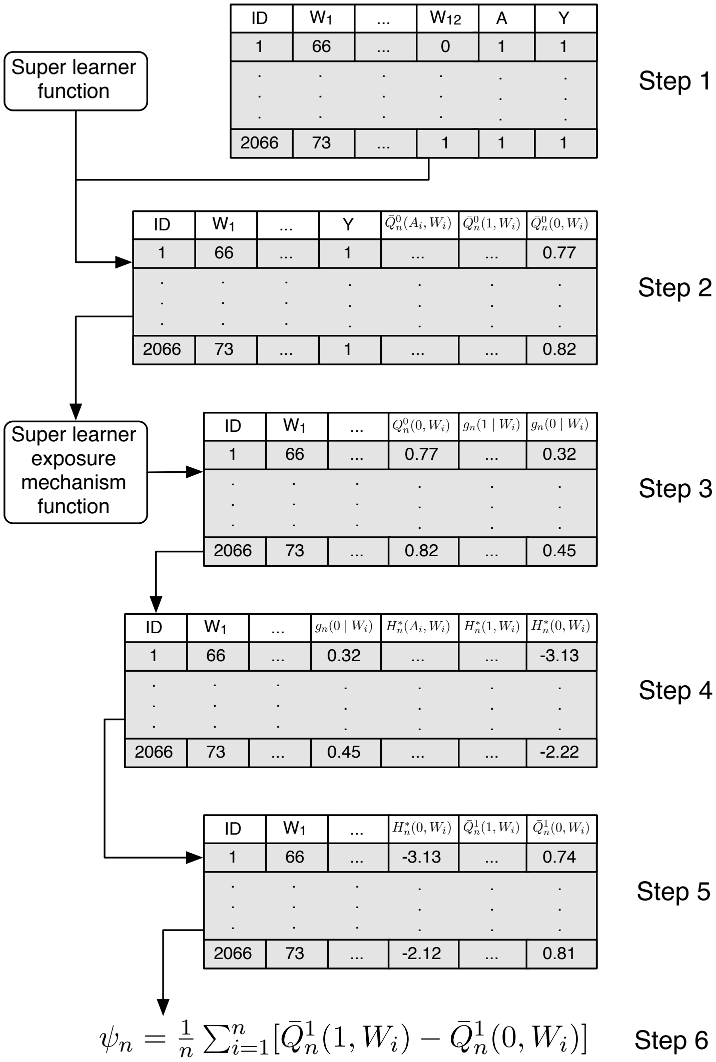


**Fig. 4.2** Flow diagram for TMLE of the risk difference in the mortality study example

**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 $z_\alpha$ denotes the $\alpha$-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 $\Phi$ 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 expressed 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 $\Delta$ is an indicator of the clinical outcome being observed. Suppose we wish to estimate the additive causal effect $E_0 Y_1 - E_0 Y_0$, 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 $\epsilon$ 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 $\epsilon$ 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.

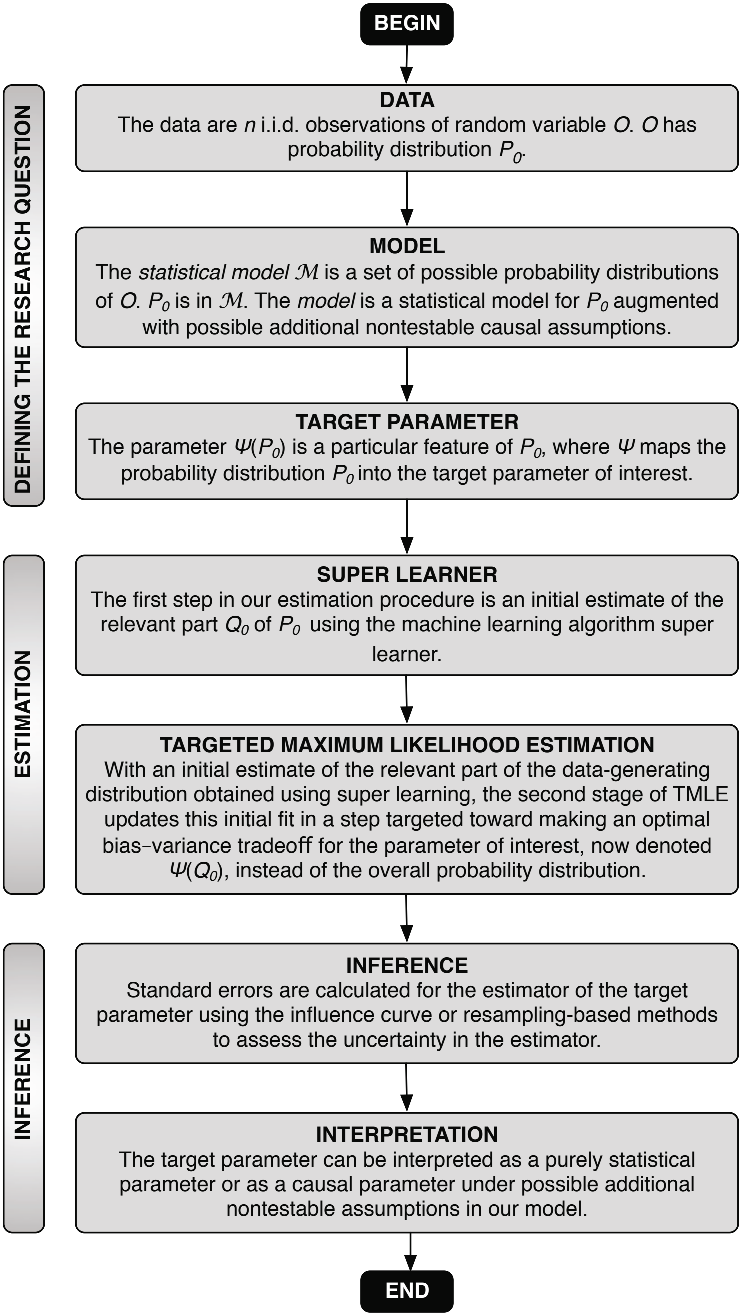


**Fig. 4.3** Road map for targeted learning

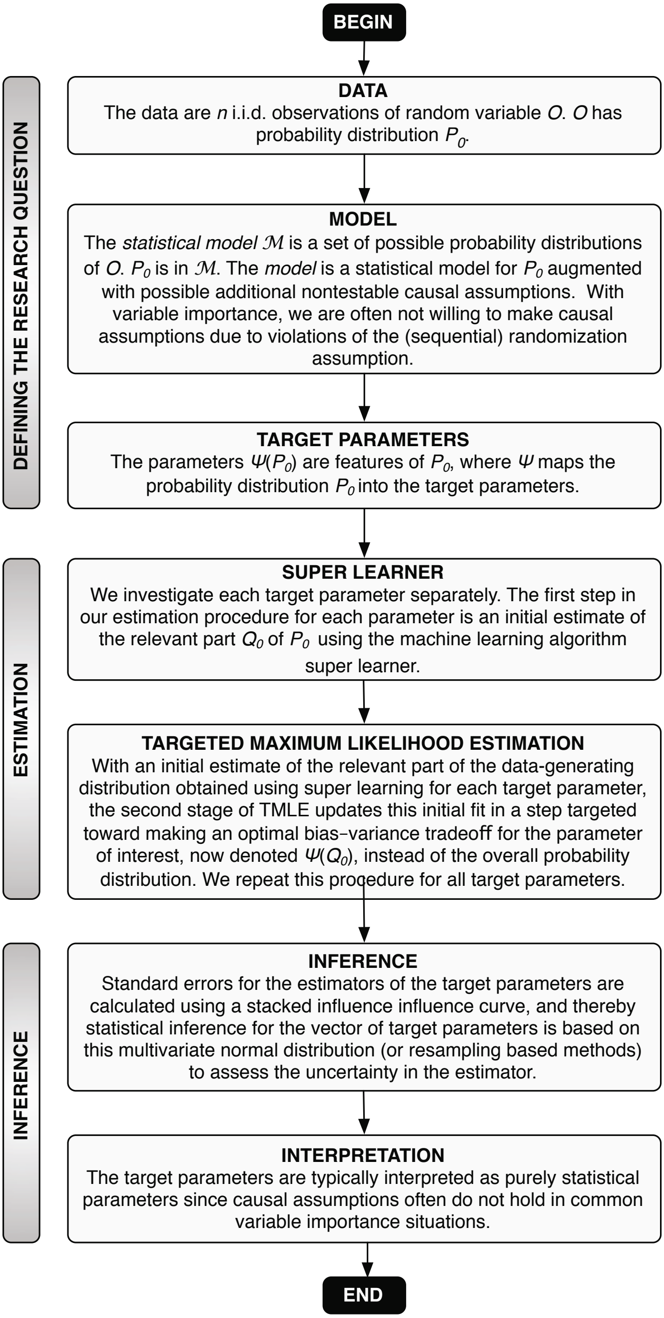


**Fig. 4.4** Road map for targeted learning of variable importance measures

## 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.

# Chapter 5
# Understanding TMLE

Sherri Rose, Mark J. van der Laan

This chapter focuses on understanding TMLE. We go into more detail than the previous chapter to demonstrate how this estimator is derived. Recall that 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.

## 5.1 Conceptual Framework

We begin the discussion of TMLE at a conceptual level to give an overall picture of what the method achieves. In Fig. 5.1 we depict a flow chart for TMLE, and in this section, we walk the reader through the illustration and provide a conceptual foundation for TMLE. We start with our observed data and some (possibly) real valued function $\Psi()$, the target parameter mapping. These two objects are our inputs. We have an initial estimator of the probability distribution of the data (or something smaller than that – the relevant portion). This is $P_n^0$ and is estimated semiparametrically using super learning. This initial estimator is typically already somewhat informed about the target parameter of interest by, for example, only focusing on fitting the relevant part $Q_0$ of $P_0$. $P_n^0$ falls within the statistical model, which is the set of all possible probability distributions of the data. $P_0$, the true probability distribution, also falls within the statistical model, since it is assumed that the statistical model is selected to represent true knowledge. In many applications the statistical model is necessarily nonparametric. We update $P_n^0$ in a particular way, in a targeted way by incorporating the target parameter mapping $\Psi$, and now denote this targeted update as $P_n^*$. If we map $P_n^*$ using our function $\Psi()$, we get our estimator $\Psi(P_n^*)$ and thereby a value on the real line. The updating step is tailored to result in values

M.J. van der Laan and S. Rose, *Targeted Learning: Causal Inference for Observational and Experimental Data*, Springer Series in Statistics, DOI 10.1007/978-1-4419-9782-1_5,

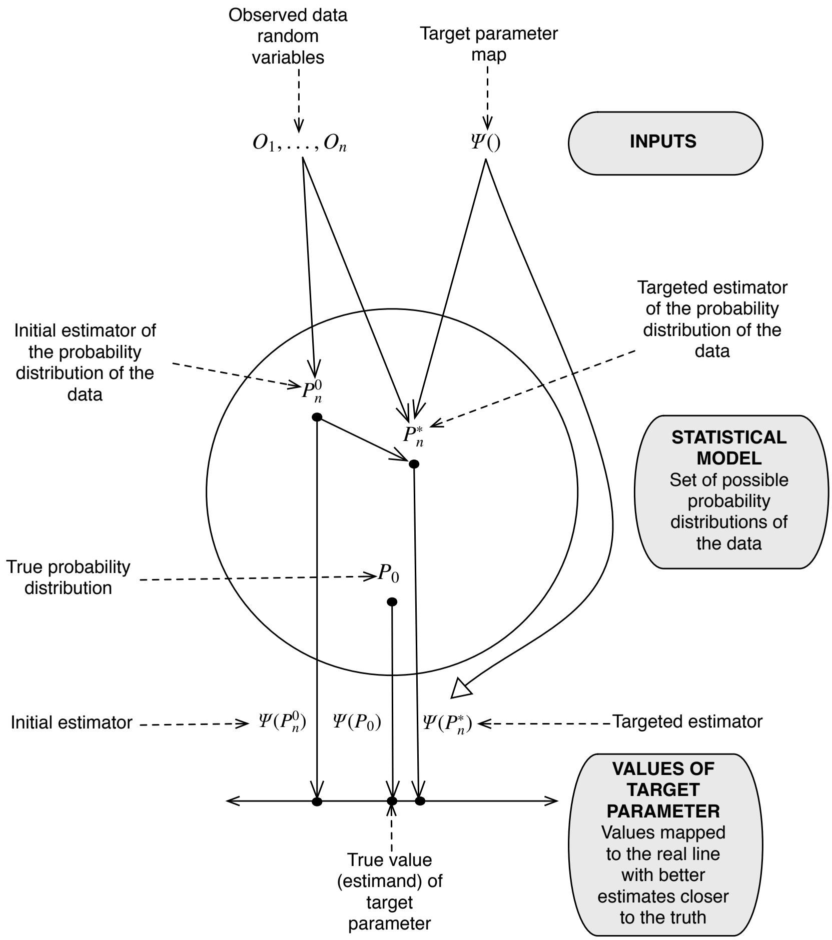


**Fig. 5.1** TMLE flow chart.

$\Psi(P_n^*)$ that are closer to the truth than the value generated using the initial estimate $P_n^0$: specifically, $\Psi(P_n^*)$ is less biased than $\Psi(P_n^0)$.

TMLE provides a concrete methodology for mapping the initial estimator $P_n^0$ into a targeted estimator $P_n^*$, which is described below in terms of an arbitrary statistical model $\mathcal{M}$ and target parameter mapping $\Psi()$ defined on this statistical model. In order to make this more accessible to the reader, we then demonstrate this general template for TMLE with a nonparametric statistical model for a univariate random variable and a survival probability target parameter. Specifically, TMLE involves the following steps:

- Consider the target parameter $\Psi : \mathcal{M} \to \mathbb{R}$. Compute its pathwise derivative at $P$ and its corresponding canonical gradient $D^*(P)$, which is also called the efficient influence curve. This object $D^*(P)$, a function of $O$ with mean zero under $P$, is now available for each possible probability distribution $P$.

- Define a loss function $L()$ so that $P \rightarrow E_0 L(P)$ is minimized at the true probability distribution $P_0$. One could select the log-likelihood loss function $L(P) = -\log P$. However, typically, this loss function is chosen so that it only depends on $P$ through a relevant part $Q(P)$ and $Q \rightarrow L(Q)$ is minimized at $Q_0 = Q(P_0)$. This loss function could also be used to construct a super-learner-based initial estimator of $Q_0$.
- For a $P$ in our model $\mathcal{M}$, define a parametric working model $\{P(\epsilon) : \epsilon\}$ with finite-dimensional parameter $\epsilon$ so that $P(\epsilon = 0) = P$, and a "score" $\frac{d}{d\epsilon} L(P(\epsilon))$ at $\epsilon = 0$ for which a linear combination of the components of this "score" equals the efficient influence curve $D^*(P)$ at $P$. Typically, we simply choose the parametric working model so that this score equals the efficient influence curve $D^*(P)$. If the loss function $L()$ only depends on $P$ through a relevant part $Q = Q(P)$, then this translates into a parametric working model $\{Q(\epsilon) : \epsilon\}$ chosen so that a linear combination of the components of the "score" $\frac{d}{d\epsilon} L(Q(\epsilon))$ at $\epsilon = 0$ equals the efficient influence curve $D^*(P)$ at $P$.
- Given an initial estimator $P_n^0$ of $P_0$, we compute $\epsilon_n^0 = \arg\min_\epsilon \sum_{i=1}^n L(P_n^0(\epsilon))(O_i)$. This yields the first step TMLE $P_n^1 = P_n^0(\epsilon_n^0)$. This process is iterated: start with $k = 1$, compute $\epsilon_n^k = \arg\min_\epsilon \sum_{i=1}^n L(P_n^k(\epsilon))(O_i)$ and $P_n^{k+1} = P_n^k(\epsilon_n^k)$, increase $k$ to $k + 1$, and repeat these updating steps until $\epsilon_n^k = 0$. The final update $P_n^K$ at the final step $K$ is denoted by $P_n^*$ and is the TMLE of $P_0$. The same algorithm can be directly applied to $Q_n^0$ of $Q_0 = Q(P_0)$ for the case that the loss function only depends on $P$ through $Q(P)$.
- The TMLE of $\psi_0$ is now the substitution estimator obtained by plugging $P_n^*$ into the target parameter mapping: $\psi_n^* = \Psi(P_n^*)$. Similarly, if $\psi_0 = \Psi(Q_0)$ and the above loss function $L()$ is a loss function for $Q_0$, then we plug the TMLE $Q_n^*$ into the target parameter mapping: $\psi_n^* = \Psi(Q_n^*)$.
- The TMLE $P_n^*$ solves the efficient influence curve equation $0 = \sum_{i=1}^n D^*(P_n^*)(O_i)$, which provides a basis for establishing the asymptotic linearity and efficiency of the TMLE $\Psi(P_n^*)$.

For further presentation of TMLE at this general level we refer the interested reader to Appendix A.

**Demonstration of TMLE template.** In this section we demonstrate the TMLE template for estimation of survival probability. Suppose we observe $n$ i.i.d. univariate random variables $O_1, \ldots, O_n$ with probability distribution $P_0$, where $O_i$ represents a time to failure such as death. Suppose that we have no knowledge about this probability distribution, so that we select as statistical model the nonparametric model $\mathcal{M}$. Let $\Psi(P) = P(O > 5)$ be the target parameter that maps any probability distribution in its survival probability at 5 years, and let $\psi_0 = P_0(O > 5)$ be our target parameter of the true data-generating distribution.

The pathwise derivative $\Psi(P(\epsilon))$ at $\epsilon = 0$ for a parametric submodel (i.e., path) $\{P_S(\epsilon) = (1 + \epsilon S(P))P : \epsilon\}$ with univariate parameter $\epsilon$ is given by

$$\frac{d}{d\epsilon}\Psi(P_S(\epsilon))\bigg|_{\epsilon=0} = E_P\{I(O > 5) - \Psi(P)\}S(P)(O).$$

Note that indeed, for any function $S$ of $O$ that has mean zero under $P$ and is uniformly bounded, it follows that $P_S(\epsilon)$ is a probability distribution for a small enough choice of $\epsilon$, so that the family of paths indexed by such functions $S$ represents a valid family of submodels through $P$ in the nonparametric model. By definition, it follows that the canonical gradient of this pathwise derivative at $P$ (relative to this family of parametric submodels) is given by $D^*(P)(O) = I(O > 5) - \Psi(P)$. The canonical gradient is also called the efficient influence curve at $P$.

We could select the log-likelihood loss function $L(P) = -\log P(O)$ as loss function. A parametric working model through $P$ is given by $P(\epsilon) = (1 + \epsilon D^*(P))P$, where $\epsilon$ is the univariate fluctuation parameter. Note that this parametric submodel includes $P$ at $\epsilon = 0$ and has a score at $\epsilon = 0$ given by $D^*(P)$, as required for the TMLE algorithm. We are now ready to define the TMLE.

Let $P_n^0$ be an initial density estimator of the density $P_0$. Let

$$\epsilon_n^0 = \arg\max_{\epsilon} \sum_{i=1}^{n} \log P_n^0(\epsilon)(O_i),$$

and let $P_n^1 = P_n^0(\epsilon_n^0)$ be the corresponding first-step TMLE of $P_0$. It can be shown that the next iteration yields $\epsilon_n^1 = 0$, so that convergence of the iterative TMLE algorithm occurs in one step (van der Laan and Rubin 2006). The TMLE is thus given by $P_n^* = P_n^1$, and the TMLE of $\psi_0$ is given by the plug-in estimator $\psi_n^* = \Psi(P_n^*) = P_n^*(O > 5)$. Since $P_n^*$ solves the efficient influence curve equation, it follows that $\psi_n^* = \frac{1}{n}\sum_{i=1}^n I(O_i > 5)$ is the empirical proportion of subjects that has a survival time larger than 5. This estimator is asymptotically linear with influence curve $D^*(P_0)$ since $\psi_n^* - \psi_0 = \frac{1}{n}\sum_{i=1}^n D^*(P_0)(O_i)$, which proves that the TMLE of $\psi_0$ is efficient for every choice of initial estimator: apparently, all bias of the initial estimator is removed by this TMLE update step.

Consider a kernel density estimator with an optimally selected bandwidth (e.g., based on likelihood-based cross-validation). Since this optimally selected bandwidth trades off bias and variance for the kernel density estimator as an estimate of the true density $P_0$, it will, under some smoothness conditions, select a bandwidth that converges to zero in sample size at a rate $n^{-1/5}$. The bias of such a kernel density estimator converges to zero at the rate $n^{-2/5}$. As a consequence, the substitution estimator of the survival function at $t$ for this kernel density estimator has a bias that converges to zero at a slower rate than $1/\sqrt{n}$ in the sample size $n$. We can conclude that the substitution estimator of a survival function at 5 years based on this optimal kernel density estimator will have an asymptotic relative efficiency of zero (!) relative to the empirical survival function at 5 years. This simple example demonstrates that a regularized maximum likelihood estimator of $P_0$ is not targeted toward the target parameter of interest and, by the same token, that current Bayesian inference is not targeted toward the target parameter. However, if we apply the TMLE step to the kernel density estimator, then the resulting TMLE of the survival function is unbiased and asymptotically efficient, and it even remains unbiased and asymptotically efficient if the kernel density estimator is replaced by an incorrect guess of the true density.

The point is: the best estimator of a density is not a good enough estimator of a particular feature of the density, but the TMLE step takes care of this.

## 5.2 Definition of TMLE in Context of the Mortality Example

This section presents the definition of TMLE in the context of our mortality example, thereby allowing the reader to derive the TMLE presented in the previous chapter. The reader may recognize the general recipe for TMLE as presented in Sect. 5.1 that can be applied in any semiparametric model with any target parameter. After having read this section, the reader might consider revisiting this general TMLE presentation. Our causal effect of interest is the causal risk difference, and the estimand is the corresponding statistical $W$-adjusted risk difference, which can be interpreted as the causal risk difference under causal assumptions. The data structure in the illustrative example is $O = (W, A, Y) \sim P_0$. TMLE follows the basic steps enumerated below, which we then illustrate in more detail.

*TMLE for the Risk Difference*

1. Estimate $\bar{Q}_0$ using super learner to generate our prediction function $\bar{Q}_n^0$. Let $Q_n^0 = (\bar{Q}_n^0, Q_{W,n})$ be the estimate of $Q_0 = (\bar{Q}_0, Q_{W,0})$, where $Q_{W,n}$ is the empirical probability distribution of $W_1, \ldots, W_n$.
2. Estimate the treatment mechanism using super learning. The estimate of $g_0$ is $g_n$.
3. Determine a parametric family of fluctuations $\{Q_n^0(\epsilon) : \epsilon\}$ of the initial estimator $Q_n^0$ with fluctuation parameter $\epsilon$, and a loss function $L(Q)$ so that a linear combination of the components of the derivative of $L(Q_n^0(\epsilon))$ at $\epsilon = 0$ equals the efficient influence curve $D^*(Q_n^0, g_n)$ at any initial estimator $Q_n^0 = (\bar{Q}_n^0, Q_{W,n}^0)$ and $g_n$. Since the initial estimate $Q_{W,n}^0$ of the marginal distribution of $W$ is the empirical distribution (i.e., nonparametric maximum likelihood estimator), the TMLE using a separate $\epsilon$ for fluctuating $Q_{W,n}^0$ and $\bar{Q}_n^0$ will only fluctuate $\bar{Q}_n^0$. The parametric family of fluctuations of $\bar{Q}_n^0$ is defined by parametric regression including a clever covariate chosen so that the above derivative condition holds with $\epsilon$ playing the role of the coefficient in front of the clever covariate. This "clever covariate" $H_n^*(A, W)$ depends on $(Q_n^0, g_n)$ only through $g_n$, and in the TMLE procedure it needs to be evaluated for each observation $(A_i, W_i)$, and at $(0, W_i)$, $(1, W_i)$.

4. Update the initial fit $\bar{Q}_n^0(A, W)$ from step 1. This is achieved by holding $\bar{Q}_n^0(A, W)$ fixed (i.e., as intercept) while estimating the coefficient $\epsilon$ for $H_n^*(A, W)$ in the parametric working model using maximum likelihood estimation. Let $\epsilon_n$ be this parametric maximum likelihood estimator. The updated regression is given by $\bar{Q}_n^1 = \bar{Q}_n^0(\epsilon_n)$. For the risk difference, no iteration is necessary, since the next iteration will not result in any change: that is, the next $\epsilon_n$ will be equal to zero. The TMLE of $Q_0$ is now $Q_n^* = (\bar{Q}_n^1, Q_{W,n}^0)$, where only the conditional mean estimator $\bar{Q}_n^0$ was updated.
5. Obtain the substitution estimator of the causal risk difference by application of the target parameter mapping to $Q_n^*$:
$$\psi_n = \Psi(Q_n^*) = \frac{1}{n}\sum_{i=1}^{n}\{\bar{Q}_n^1(1, W_i) - \bar{Q}_n^1(0, W_i)\}.$$
6. Calculate standard errors based on the influence curve of the TMLE $\psi_n$, and then calculate $p$-values and confidence intervals.

There are several concepts in this enumerated step-by-step list that may be somewhat opaque for the reader: the parametric working model coding the fluctuations of the initial estimator, the corresponding clever covariate, the efficient influence curve, and the influence curve. We expand upon the list, including these topics, below. For the nontechnical reader, we provide gray boxes so that you can read these to understand the essential topics relevant to each step. The white boxes outlined in black contain additional technical information for the more theoretical reader.

### 5.2.1 Estimating $\bar{Q}_0$

The first step in TMLE is obtaining an estimate $\bar{Q}_n^0$ for $\bar{Q}_0$. This initial fit is achieved using super learning, avoiding assuming a misspecified parametric statistical model.

### 5.2.2 Estimating $g_0$

The TMLE procedure uses the estimate of $\bar{Q}_0$ obtained above in conjunction with an estimate of $g_0$. We estimate $g_0$ with $g_n$, again using super learning.

### 5.2.3 Determining the Efficient Influence Curve $D^*(P)$

To obtain such a parametric working model to fluctuate the initial estimator $Q_n^0$ we need to know the efficient influence curve of the target parameter mapping at a particular $P$ in the statistical model. This is a mathematical exercise that takes as input the definition of the statistical model $\mathcal{M}$ (i.e, the nonparametric model) and the target parameter mapping from this statistical model to the real line (i.e., $\Psi : \mathcal{M} \to \mathbb{R}$). We refer to Appendix A for required background material. It follows that the efficient influence curve at $P_0$ only depends on $(Q_0, g_0)$ and is given by

$$D^*(Q_0, g_0)(W, A, Y) = \left(\frac{I(A = 1)}{g_0(1 \mid W)} - \frac{I(A = 0)}{g_0(0 \mid W)}\right)(Y - \bar{Q}_0(A, W)) \\ + \bar{Q}_0(1, W) - \bar{Q}_0(0, W) - \Psi(Q_0).$$

**More on the efficient influence curve.** Calculation of the efficient influence curve, and of components of the efficient influence curve, requires calculations of projections of an element onto a subspace within a Hilbert space. These projections are defined in the Hilbert space $L_0^2(P)$ of functions of $O$ that have mean zero under $P$ endowed with an inner product $\langle S_1, S_2\rangle_P = E_P S_1(O) S_2(O)$, being the covariance of two functions of $O$. Two elements in an Hilbert space are orthogonal if the inner product equals zero: so two functions of $O$ are defined as orthogonal if their correlation or covariance equals zero. Recall that a projection of a function $S$ onto a subspace of $L_0^2(P)$ is defined as follows: (1) the projection is an element of the subspace and (2) the difference of $S$ minus the projection is orthogonal to the subspace. The subspaces on which one projects are so-called tangent spaces and subtangent spaces. The tangent space at $P$ is defined as the closure of the linear span of all scores of submodels through $P$. The tangent space is a subspace of $L_0^2(P)$. The tangent space of a particular variation-independent parameter of $P$ is defined as the closure of the linear span of all scores of submodels through $P$ that only vary this particular factor. We can denote the tangent spaces by $T(P)$ and a projection of a function $S$ onto a $T(P)$ by $\Pi(S \mid T(P))$.

### 5.2.4 Determining the Fluctuation Working Model

Now, can we slightly modify the initial estimator $\bar{Q}_n^0$ to reduce bias for the additive causal effect? Let $Q_{W,n}^0$ be the empirical probability distribution of $W_1, \ldots, W_n$. We refer to the combined conditional probability distribution of $Y$ and the marginal probability distribution of $W$ as $Q_0$. $Q_n^0 = (\bar{Q}_n^0, Q_{W,n}^0)$ denotes the initial estimator of this $Q_0$. We also remind the reader that the target parameter $\psi_0$ only depends on

$P_0$ through $\bar{Q}_0$ and $Q_{W,0}$. Since the empirical distribution $Q^0_{W,n}$ is already a nonparametric maximum likelihood estimator of the true marginal probability distribution of $W$, for the sake of bias reduction for the target parameter, we can focus on only updating $\bar{Q}^0_n$, as explained below.

We want to reduce the bias of our initial estimator, where the initial estimator is a random variable that has bias and variance. We only need to update $\bar{Q}^0_n$ since the empirical distribution $Q^0_{W,n}$ is a nonparametric maximum likelihood estimator (and can thus not generate bias for our target parameter).

Our parametric working model is denoted as $\{\bar{Q}^0_n(\epsilon) : \epsilon\}$, which is a small parametric statistical model, a one-dimensional submodel that goes through the initial estimate $\bar{Q}^0_n(A, W)$ at $\epsilon = 0$. If we use the log-likelihood loss function

$$L(\bar{Q})(O) = -\log \bar{Q}(A, W)^Y (1 - \bar{Q}(A, W))^{1-Y},$$

then the parametric working model for fluctuating the conditional probability distribution of $Y$, given $(A, W)$, needs to have the property

$$\frac{d}{d\epsilon} \log \bar{Q}^0_n(\epsilon)(A, W)^Y (1 - \bar{Q}^0_n(A, W))^{1-Y}|_{\epsilon=0} = D^*_Y(Q^0_n, g_n)(W, A, Y), \tag{5.1}$$

where $D^*_Y(Q^0_n, g_n)$ is the appropriate component of the efficient influence curve $D^*(Q^0_n, g_n)$ of the target parameter mapping at $(Q^0_n, g_n)$. Formally, the appropriate component $D^*_Y$ is the component of the efficient influence curve that equals a score of a fluctuation of a conditional distribution of $Y$, given $(A, W)$. These components of the efficient influence curve that correspond with scores of fluctuations that only vary certain parts of factors of the probability distribution can be computed with Hilbert space projections. We provide the required background and tools in Appendix A and various subsequent chapters.

**More on fluctuating the initial estimator.** If the target parameter $\psi_0$ depends on different variation-independent parts $(Q_{W,0}, \bar{Q}_0)$ of the probability distribution $P_0$, then one can decide to fluctuate the initial estimators $(Q^0_{W,n}, \bar{Q}_n)$ with separate submodels and separate loss functions $L(Q_W) = -\log Q_W$ and $L(\bar{Q})$, respectively. The submodels $\{Q^0_{W,n}(\epsilon) : \epsilon\}$, $\{\bar{Q}_n(\epsilon) : \epsilon\}$ and their corresponding loss functions $L(Q_W)$ and $L(\bar{Q})$ need to be chosen such that a linear combination of the components of the derivative $\frac{d}{d\epsilon} L(Q^0_n(\epsilon))\big|_{\epsilon=0}$ equals $D^*(Q^0_n, g_n)$ for the sum-loss function $L(Q) = L(Q_W) + L(\bar{Q})$. This corresponds with requiring that each of the two loss functions generates a "score" so that the sum of these two "scores" equals the efficient influence curve. If the initial estimator $Q^0_{W,n}$ is a nonparametric maximum likelihood estimator, the TMLE using a separate $\epsilon_1$ and $\epsilon_2$ for the two submodels will not update $Q^0_{W,n}$.

Following the protocol of TMLE, we also need to fluctuate the marginal distribution of $W$. For that purpose we select as loss function of $Q_{W,0}$ the log-likelihood loss function $-\log Q_W$. Then we would select a parametric working model coding fluctuations $Q^0_{W,n}(\epsilon)$ of $Q^0_{W,n}$ so that

$$\frac{d}{d\epsilon}\log Q^0_{W,n}(\epsilon)\Big|_{\epsilon=0} = D^*_W(Q^0_n, g_n),$$

where $D^*_W$ is the component of the efficient influence curve that is a score of a fluctuation of the marginal distribution of $W$.

**Tangent spaces.** Since $Q_W$ and $\bar{Q}$ represent parameters of different factors $P_W$ and $P_{Y|A,W}$ in a factorization of $P = P_W P_{A|W} P_{Y|A,W}$, these components $D^*_W(P)$ and $D^*_Y(P)$ can be defined as the projection of the efficient influence curve $D^*(P)$ onto the tangent space of $P_W$ at $P$ and $P_{Y|A,W}$ at $P$, respectively. The tangent space $T_W$ of $P_W$ is given by all functions of $W$ with mean zero. The tangent space $T_Y$ of $P_{Y|A,W}$ is given by all functions of $W, A, Y$ for which the conditional mean, given $A, W$, equals zero. The tangent space $T_A$ of $P_{A|W}$ is given by all functions of $A, W$, with conditional mean zero, given $W$. These three tangent spaces are orthogonal, as a general consequence of the factorization of $P$ into the three factors. The projection of a function $S$ onto these three tangent spaces is given by $\Pi(S \mid T_W) = E_P(S(O) \mid W)$, $\Pi(S \mid T_Y)) = S(O) - E_P(S(O) \mid A, W)$, and $\Pi(S \mid T_A) = E_P(S(O) \mid A, W) - E_P(S \mid W)$, respectively. From these projection formulas and setting $S = D^*(P)$, the explicit forms of $D^*_W(P) = \Pi(D^*(P) \mid T_W)$ and $D^*_Y(P) = \Pi(D^*(P) \mid T_Y)$ can be calculated as provided below, and for each choice of $P$. It also follows that the projection of $D^*(P)$ onto the tangent space of $P_{A|W}$ equals zero: $\Pi(D^*(P) \mid T_A) = 0$. The latter formally explains that the TMLE does not require fluctuating the initial estimator of $g_0$. It follows that the efficient influence curve $D^*(P)$ at $P$ can be decomposed as:

$$D^*(P) = D^*_Y(P) + D^*_W(P).$$

Our loss function for $Q$ is now $L(Q) = L(\bar{Q}) + L(Q_W)$, and with this parametric working model coding fluctuations $Q^0_n(\epsilon) = (Q^0_{W,n}(\epsilon), \bar{Q}^0_n(\epsilon))$ of $Q^0_n$, we have that the derivative of $\epsilon \to L(Q^0_n(\epsilon))$ at $\epsilon = 0$ equals the efficient influence curve at $(Q^0_n, g_n)$. If we use different $\epsilon$ for each component of $Q^0_n$, then the two derivatives span the efficient influence curve, since the efficient influence curve equals the sum of the two scores $D^*_Y$ and $D^*_W$. Either way, the derivative condition is satisfied:

$$\langle \frac{d}{d\epsilon} L(Q^0_n(\epsilon))\Big|_{\epsilon=0} \rangle \supset D^*(Q^0_n, g_n), \tag{5.2}$$

where $D^*(Q_n^0, g_n) = D_Y^*(Q_n^0, g_n) + D_W^*(Q_n^0, g_n)$. Here we used the notation $\langle(h_1, \ldots, h_k)\rangle$ for the linear space consisting of all linear combinations of the functions $h_1, \ldots, h_k$. That is, the task of obtaining a loss function and parametric working model for fluctuating $Q_n^0$ so that the derivative condition holds has been completed.

Due to this property (5.2) of the parametric working model, the TMLE has the important feature that it solves the efficient influence curve equation $0 = \sum_i D^*(Q_n^*, g_n)(O_i)$ (also called the efficient score equation). Why is this true? Because at the next iteration of TMLE, the parametric maximum likelihood estimator $\epsilon_n = 0$, and a parametric maximum likelihood estimator solves its score equation, which exactly yields this efficient score equation. This is a strong feature of the procedure as it implies that TMLE is double robust and (locally) efficient under regularity conditions. In other words, TMLE is consistent and asymptotically linear if either $Q_n$ or $g_n$ is a consistent estimator, and if both estimators are asymptotically consistent, then TMLE is asymptotically efficient.

However, if one uses a separate $\epsilon_W$ and $\epsilon$ for the two parametric working models through $Q_{W,n}^0$ and $\bar{Q}_n^0$, respectively, then the maximum likelihood estimator of $\epsilon_W$ equals zero, showing that TMLE will only update $\bar{Q}_n^0$. Therefore, it was never necessary to update the part of $Q_n^0$ that was already nonparametrically estimated.

If the initial estimator of $Q_{W,0}$ is a nonparametric maximum likelihood estimator, then the TMLE does not update this part of the initial estimator $Q_n^0$.

Of course, we have not been explicit yet about how to construct this submodel $\bar{Q}_n^0(\epsilon)$ through $\bar{Q}_n^0$. For that purpose, we now note that $D_Y^*(Q_n^0, g_n)$ equals a function $H_n^*(A, W)$ times the residual $(Y - \bar{Q}_n^0(A, W))$, where

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

Here $I(A = 1)$ is an indicator variable that takes the value 1 when $A = 1$. One can see that for $A = 1$ the second term disappears, and for $A = 0$ the first term disappears.

It can be shown (and it is a classical result for parametric logistic main term regression in a parametric statistical model) that the score of a coefficient in front of a covariate in a logistic linear regression in a parametric statistical model for a conditional distribution of a binary $Y$ equals the covariate times the residual. Therefore, we can select the following parametric working model for fluctuating the initial estimate of the conditional probability distribution of $Y$, given $(A, W)$, or, equivalently, for the estimate of the probability of $Y = 1$, given $(A, W)$:

$$\bar{Q}_n^0(\epsilon)(Y = 1 \mid A, W) = \frac{1}{1 + \exp\left(-\log \frac{\bar{Q}_n^0}{(1-\bar{Q}_n^0)}(A, W) - \epsilon H_n^*(A, W)\right)}.$$

By this classical result, it follows that indeed the score of $\epsilon$ of this univariate logistic regression submodel at $\epsilon = 0$ equals $D^*_Y(Q^0_n, g_n)$. That is, we now have really fully succeeded in finding a parametric submodel through the initial estimator $Q^0_n$ that satisfies the required derivative condition. Since $H^*_n(A, W)$ now just plays the role of a covariate in a logistic regression, using an offset, this explains why we call the covariate $H^*_n(A, W)$ a clever covariate.

**More on constructing the submodel.** If one needs a submodel through an initial estimator of a conditional distribution of a binary variable $Y$, given a set of parent variables $Pa(Y)$, and it needs to have a particular score $D^*_Y$, then one can define this submodel as a univariate logistic regression model, using the initial estimator as offset, with univariate clever covariate defined as $H^*(Pa(Y)) = E(D^*_Y \mid Y = 1, Pa(Y)) - E(D^*_Y \mid Y = 0, Pa(Y))$. Application of this general result to the above setting yields the clever covariate $H^*(A, W)$ presented above.

If our goal was to target $P_0(Y_1 = 1)$ or $P_0(Y_0 = 1)$, then going through the same protocol for the TMLE shows that one would use as clever covariate

$$H^*_{0,n}(A, W) \equiv \left(\frac{I(A = 0)}{g_n(A = 0 \mid W)}\right) \text{ or } H^*_{1,n}(A, W) \equiv \left(\frac{I(A = 1)}{g_n(A = 1 \mid W)}\right).$$

By targeting these two parameters simultaneously, using a two-dimensional clever covariate with coefficients $\epsilon_1, \epsilon_2$, one automatically obtains a valid TMLE for parameters that are functions of these two marginal counterfactual probabilities, such as a causal relative risk and causal odds ratio.

By computing the TMLE that targets a multidimensional target parameter, one also obtains a valid TMLE for any (say) univariate summary measure of the multidimensional target parameter. By valid we mean that this TMLE will still satisfy the same asymptotic properties, such as efficiency and double robustness, as the TMLE that directly targets the particular summary measure. The TMLE that targets the univariate summary measure of the multidimensional parameter may have a better finite sample performance than the TMLE that targets the whole multidimensional target parameter, in particular, if the dimension of the multidimensional parameter is large.

### 5.2.5 Updating $\bar{Q}^0_n$

We first perform a logistic linear regression of $Y$ on $H^*_n(A, W)$ where $\bar{Q}^0_n(A, W)$ is held fixed (i.e., used as an offset), and an additional intercept is suppressed in order to estimate the coefficient in front of $H^*_n(A, W)$, denoted $\epsilon$. The TMLE procedure is then able to incorporate information from $g_n$, through $H_n^*(A, W)$, into an updated regression. It does this by extracting $\epsilon_n$, the maximum likelihood estimator of $\epsilon$, from the fit described above, and updating the estimate $\bar{Q}_n^0$ according to the logistic regression working model. This updated regression is then given by $\bar{Q}_n^1$:

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

One iterates this updating process until the next $\epsilon_n = 0$ or has converged to zero, but, in this example, convergence is achieved in one step. The TMLE of $Q_0$ is now $Q_n^* = (Q_{W,n}^0, \bar{Q}_n^1)$. Note that this step is equivalent to $(\epsilon_{1n}, \epsilon_{2n}) = \arg\min_{\epsilon_1,\epsilon_2} \sum_i L(Q_n^0(\epsilon_1, \epsilon_2))(O_i)$, and setting $Q_n^1 = Q_n^0(\epsilon_{1n}, \epsilon_{2n})$, where, as noted above, $\epsilon_{1n} = 0$, so that only $\bar{Q}_n^0$ is updated.

Given a parametric working model $Q_n^0(\epsilon)$ with fluctuation parameter $\epsilon$, and a loss function $L(Q)$ satisfying (5.2), the first-step TMLE is defined by determining the minimum $\epsilon_n^0$ of $\sum_{i=1}^n L(Q_n^0(\epsilon))(O_i)$ and setting $Q_n^1 = Q_n^0(\epsilon_n^0)$. This updating process is iterated until convergence of $\epsilon_n^k = \arg\min_\epsilon \sum_{i=1}^n L(Q_n^k(\epsilon))$ to zero, and the final update $Q_n^*$ is referred to as the TMLE of $Q_0$. In this case, the next $\epsilon_n^1 = 0$, so that convergence is achieved in one step and $Q_n^* = Q_n^1$.

### 5.2.6 Estimating the Target Parameter

The estimate $\bar{Q}_n^* = \bar{Q}_n^1$ obtained in the previous step is now plugged into our target parameter mapping, together with the empirical distribution of $W$, resulting in the targeted substitution estimator given by

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

This mapping is 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.

### 5.2.7 Calculating Standard Errors

The calculation of standard errors for TMLE can be based on the central limit theorem, relying on $\delta$-method conditions. (See Appendix A for an advanced introduction to these topics.) Under such regularity conditions, the asymptotic behavior of the estimator, that is, its asymptotic normal limit distribution, is completely characterized by the so-called influence curve of the estimator in question. In our example, we need to know the influence curve of the TMLE of its estimand.

Note that, in order to recognize that an estimator is a random variable, an estimator should be represented as a mapping from the data into the parameter space, where the data $O_1, \ldots, O_n$ can be represented by the empirical probability distribution function $P_n$. Therefore, let $\hat{\Psi}(P_n)$ be the TMLE described above. Since the TMLE is a substitution estimator, we have $\hat{\Psi}(P_n) = \Psi(P_n^*)$ for a targeted estimator $P_n^*$ of $P_0$. An estimator $\hat{\Psi}(P_n)$ of $\psi_0$ is asymptotically linear with influence curve $IC(O)$ if it satisfies:

$$\sqrt{n}(\hat{\Psi}(P_n) - \psi_0) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} IC(O_i) + o_{P_0}(1).$$

Here the remainder term, denoted by $o_{P_0}(1)$, is a random variable that converges to zero in probability when the sample size converges to infinity. The influence curve $IC(O)$ is a random variable with mean zero under $P_0$.

**More on estimators and the influence curve.** An estimator $\hat{\Psi}(P_n)$ is a function $\hat{\Psi}$ of the empirical probability distribution function $P_n$. Specifically, one can express the estimator as a function $\hat{\Psi}$ of a large family of empirical means $1/n \sum_{i=1}^{n} f(O_i)$ of functions $f$ of $O$ varying over a class of functions $\mathcal{F}$. We say the estimator is a function of $P_n = (P_n f : f \in \mathcal{F})$, where we use the notation $P_n f \equiv 1/n \sum_{i=1}^{n} f(O_i)$. By proving that the estimator is a differentiable function $\hat{\Psi}$ of $P_n = (P_n f : f \in \mathcal{F})$ at $P_0 = (P_0 f : f \in \mathcal{F})$, and that a uniform central limit theorem applies to $P_n$ based on empirical process theory, it follows that the estimator minus its estimand $\psi_0 = \hat{\Psi}(P_0)$ behaves in first order as an empirical mean of $IC(O_i)$: we write $\hat{\Psi}(P_n) - \psi_0 = (P_n - P_0)IC + o_P(1/\sqrt{n})$. This function $IC(O)$ is called the influence curve of the estimator, and it is uniquely determined by the derivative of $\hat{\Psi}$. Specifically, $IC(O) = \sum_{f \in \mathcal{F}} \frac{d}{dP_0 f} \hat{\Psi}((P_0 f : f)(f(O) - P_0 f)$, where, formally, the $\sum$ becomes an integral when $\mathcal{F}$ is not finite.

Asymptotic linearity is a desirable property as it indicates that the estimator behaves like an empirical mean, and, as a consequence, its bias converges to zero in sample size at a rate faster than $1/\sqrt{n}$, and, for $n$ large enough, it is approximately normally distributed. The influence curve of an estimator evaluated as a function in $O$ measures how robust the estimator is toward extreme values. The influence curve $IC(O)$ has mean zero under sampling from the true probability distribution $P_0$, and its (finite) variance is the asymptotic variance of the standardized estimator $\sqrt{n}(\hat{\Psi}(P_n) - \psi_0)$.

In other words, the variance of $\hat{\Psi}(P_n)$ is well approximated by the variance of the influence curve, divided by sample size $n$. If $\psi_0$ is multivariate, then the covariance matrix of $\hat{\Psi}(P_n)$ is well approximated by the covariance matrix of the multivariate influence curve divided by sample size $n$. More importantly, the probability distribution of $\hat{\Psi}(P_n)$ is well approximated by a normal distribution with mean $\psi_0$ and the covariance matrix of the influence curve, divided by sample size.

An estimator is asymptotically efficient if its influence curve is equal to the efficient influence curve, $IC(O) = D^*(O)$. The influence curve of the TMLE indeed equals $D^*$ if $Q_n^*$ is a consistent estimator of $Q_0$, and $g_n$ is a consistent estimator of $g_0$. A complete technical understanding of influence curve derivation is not necessary to implement the TMLE procedure. However, we provide Appendix A for a detailed methodology for deriving the influence curve of an estimator.

**More on asymptotic linearity and efficiency.** The TMLE is a consistent estimator of $\psi_0$ if either $\bar{Q}_n$ is consistent for $\bar{Q}_0$ or $g_n$ is consistent for $g_0$. The TMLE is asymptotically linear under additional conditions. For a detailed theorem establishing asymptotic linearity and efficiency of the TMLE, we refer the reader to Chap. 27. In particular, if for some $\delta > 0$, $\delta < g_0(1 \mid W) < 1 - \delta$, and the product of the $L^2$-norm of $\bar{Q}_n - \bar{Q}_0$ and the $L^2$-norm of $g_n - g_0$ converges to zero at faster rate than $1/\sqrt{n}$, then the TMLE is asymptotically efficient. If $g_n$ is a consistent estimator of $g_0$, then the influence curve of the TMLE $\hat{\Psi}(P_n)$ equals $IC = D^*(Q^*, g_0) - \Pi(D^*(Q^*, g_0) \mid T_g)$, the efficient influence curve at the possibly misspecified limit of $Q_n^*$ minus its projection on the tangent space of the model for the treatment mechanism $g_0$. The projection term makes $D^*(Q^*, g_0)$ a conservative working influence curve, and the projection term equals zero if either $Q^* = Q_0$ or $g_0$ was known and $g_n = g_0$.

From these formal asymptotic linearity results for the TMLE it follows that if $g_n$ is a consistent estimator of $g_0$, then the TMLE $\hat{\Psi}(P_n)$ is asymptotically linear with an influence curve that can be conservatively approximated by $D^*(Q^*, g_0)$, where $Q^*$ denotes the possibly misspecified estimand of $Q_n^*$. If $g_0$ was known, as in a randomized controlled trial, and $g_n$ was not estimated, then the influence curve of the TMLE equals $D^*(Q^*, g_0)$. If, on the other hand, $g_n$ was estimated under a correctly specified model for $g_0$, then the influence curve of the TMLE has a smaller variance than the variance of $D^*(Q^*, g_0)$, except if $Q^* = Q_0$, in which case the influence curve of the TMLE equals the efficient influence curve $D^*(Q_0, g_0)$. As a consequence, we can use as a working estimated influence curve for the TMLE

$$IC_n(O) = \left( \frac{I(A = 1)}{g_n(1 \mid W)} - \frac{I(A = 0)}{g_n(0 \mid W)} \right) (Y - \bar{Q}_n^1(A, W)) + \bar{Q}_n^1(1, W) - \bar{Q}_n^1(0, W) - \psi_n.$$

Even if $\bar{Q}_n^1$ is inconsistent, but $g_n$ is consistent, this influence curve can be used to obtain an asymptotically *conservative* estimator of the variance of the TMLE

$\hat{\Psi}(P_n)$. This is very convenient since the TMLE requires calculation of $D^*(Q_n^*, g_n)$, and apparently we can use the latter as influence curve to estimate the normal limit distribution of the TMLE.

If one assumes that $g_n$ is a consistent maximum-likelihood-based estimator of $g_0$, then one can (asymptotically) conservatively estimate the variance of the TMLE with the sample variance of the estimated efficient influence curve $D^*(Q_n^*, g_n)$.

An estimate of the asymptotic variance of the standardized TMLE, $\sqrt{n}(\hat{\Psi}(P_n) - \psi_0)$, viewed as a random variable, using the estimate of the influence curve $IC_n(O)$ is thereby given by

$$\sigma_n^2 = \frac{1}{n} \sum_{i=1}^{n} IC_n^2(o_i).$$

## 5.3 Foundation and Philosophy of TMLE

TMLE in semiparametric statistical models for $P_0$ is the extension of maximum likelihood estimation in parametric statistical models. Three key ingredients are needed for this extension. Firstly, one needs to define the parameter of interest semiparametrically as a function of the data-generating distribution varying over the (large) semiparametric statistical model. Many practitioners are used to thinking of their parameter in terms of a regression coefficient, but that luxury is not available in semi- or nonparametric statistical models. Instead, one has to carefully think of what feature of the distribution of the data one wishes to target.

Secondly, one needs to estimate the true distribution $P_0$, or at least its relevant factor or portion as needed to evaluate the target parameter, and this estimate should respect the actual semiparametric statistical model. As a consequence, nonparametric maximum likelihood estimation is often ill defined or results in a complete overfit, and thereby results in estimators of the target parameter that are too variable. We discussed this issue in Chap. 3. The theoretical results obtained for the cross-validation selector (discrete super learner) inspired the general super learning methodology for estimation of probability distributions of the data, or factors of other high-dimensional parameters of the probability distributions of the data. In the sequel, a reference to a true probability distribution of the data is meant to refer to this relevant part of the true probability distribution of the data. This super learning methodology takes as input a collection of candidate estimators of the distribution of the data and then uses cross-validation to determine the best weighted combination of these estimators. It is assumed or arranged that the loss function is uniformly bounded so that oracle results for the cross-validation selector apply. The super learning methodology results now in an estimator of the distribution of the data that will be used as an initial estimator in the TMLE procedure. The oracle results for this super learner teach us that the initial estimator is optimized with respect to a global loss function such as the log-likelihood loss function and is thereby not targeted toward the target parameter, $\Psi(P_0)$. That is, it will be too biased for $\Psi(P_0)$ due to a bias–variance tradeoff with respect to the more ambitious full $P_0$ (or relevant portion thereof) instead of having used a bias–variance tradeoff with respect to $\Psi(P_0)$. The targeted maximum likelihood step is tailored to remove bias due to the nontargeting of the initial estimator.

The targeted maximum likelihood step involves now updating this initial (super-learning-based) estimator $P_n^0$ of $P_0$ to tailor its fit to estimation of the target $\psi_0$, the value of the parameter $\Psi(P_0)$. This is carried out by determining a cleverly chosen parametric working model modeling fluctuations $P_n^0(\epsilon)$ of the initial estimator $P_n^0$ with a (say) univariate fluctuation parameter $\epsilon$. The value $\epsilon = 0$ corresponds with no fluctuation so that $P_n^0(0) = P_n^0$. One now estimates $\epsilon$ with maximum likelihood estimation, treating the initial estimator as a fixed offset, and updates the initial estimator accordingly. If needed, this updating step is iterated to convergence, and the final update $P_n^*$ is called the TMLE of $P_0$, while the resulting substitution estimator $\hat{\Psi}(P_n^*)$ of $\Psi(P_0)$ is the TMLE of $\psi_0$. This targeted maximum likelihood step thus uses a parametric maximum likelihood estimator, accordingly to a cleverly chosen parametric working model that includes the initial estimator, to obtain a bias reduction for the target $\Psi(P_0)$.

This is not just any parametric working model. That is, we wish to select a parametric working model such that the parametric maximum likelihood estimator is maximally effective in removing bias for the target parameter, at minimal increase in variance. So if $\epsilon_n$ is the parametric maximum likelihood estimator of $\epsilon$, then we want the mean squared error of $\Psi(P_n^0(\epsilon_n)) - \psi_0$ to be as small as possible. We want this parametric working model to really listen to the information in the data that is relevant for the target parameter. In fact, we would like the parametric maximum likelihood estimator to be as responsive to the information in the data that is relevant for the target parameter as an estimator that is asymptotically efficient in the semiparametric model.

To get insight into what kind of choice of parametric working model may be as adaptive to such target-parameter-specific features in the data as a semiparametric efficient estimator, we make the following observations. Suppose one is interested in determining the parametric working model coding fluctuations $P_0(\epsilon)$ of $P_0$ so that the maximum likelihood estimator of $\psi_0 = \Psi(P_0(\epsilon = 0))$ according to this parametric working model is asymptotically equivalent to an efficient estimator in the large semiparametric model. Note that this parametric working model is not told that the true value of $\epsilon$ equals zero. It happens to be the case that from an asymptotic efficiency perspective this can be achieved as follows. Among all possible parametric working models that code fluctuations $P_0(\epsilon)$ of the true $P_0$ we chose the one for which the Cramer–Rao lower bound for the target parameter $\Psi(P_0(\epsilon))$ at $\epsilon = 0$ is equivalent to the semiparametric information bound for the target parameter at $P_0$. The Cramer–Rao lower bound for a parametric working model $P_0(\epsilon)$ is given by

$$\frac{\left\{\frac{d}{d\epsilon}\Psi(P_0(\epsilon))\Big|_{\epsilon=0}\right\}^2}{I(0)},$$

where $I(0)$ denotes the variance of the score of the parametric working model at $\epsilon = 0$. In parametric model theory $I(0)$ is called the information at parameter value 0. The semiparametric information bound for the target parameter at $P_0$ is defined as the supremum over all these possible Cramer–Rao lower bounds for the parametric working models. That is, the semiparametric information bound is defined as the Cramer–Rao lower bound for the hardest parametric working model. Thus, the parametric working model for which the parametric maximum likelihood estimator is as responsive to the data with respect to the target parameter as a semiparametric efficient estimator is actually given by this hardest parametric working model. Indeed, the TMLE selects this hardest parametric working model, but through $P_n^0$.

Note also that this hardest working parametric model can also be interpreted as the one that maximizes the change of the target parameter relative to a change $P_0(\epsilon) - P_0$ under small amounts of fluctuations. Thus this hardest working parametric model through an initial estimator $P_n^0$ will maximize the change of the target parameter relative to the initial value $\Psi(P_n^0)$ for small values of $\epsilon$.

Beyond the practical appeal of this TMLE update that uses the parametric likelihood to fit the target parameter of interest, an important feature of the TMLE is that it solves the efficient influence curve equation, also called the efficient score equation, of the target parameter. We refer the reader to Sect. 5.2 and Appendix A for relevant material on the efficient influence curve. For now, it suffices to know that an estimator is semiparametric efficient if the estimator minus the true target parameter behaves as an empirical mean of $D^*(P_0)(O_i)$, $i = 1, \ldots, n$, showing the incredible importance of this transformation $D^*(P_0)$ of $O$, which somehow captures all the relevant information of $O$ for the sake of learning the statistical parameter $\Psi(P_0)$. If $D^*(P)(O)$ is the efficient influence curve at $P$, a possible probability distribution for $O$ in the statistical model, and $P_n^*$ is the TMLE of $P_0$, then, $0 = \sum_{i=1}^n D^*(P_n^*)(O_i)$.

Just as a parametric maximum likelihood estimator solves a score equation by virtue of its maximizing the likelihood over the unknown parameters, a TMLE solves the target-parameter-specific score equation for the target parameter by virtue of maximizing the likelihood in a targeted direction. This can then be used to establish that the TMLE is asymptotically efficient if the initial estimator is consistent and remarkably robust in the sense that for many data structures and semiparametric statistical models, the TMLE of $\psi_0$ remains consistent even if the initial estimator is inconsistent. By using submodels that have a multivariate fluctuation parameter $\epsilon$, the TMLE will solve the score equation implied by each component of $\epsilon$. In this manner, one can obtain TMLEs that solve not only the efficient influence curve/efficient score equation for the target parameter, but also an equation that characterizes other interesting properties, such as being an imputation estimator (Gruber and van der Laan 2010a).

In particular, in semiparametric models used to define causal effect parameters, the TMLE is a double robust estimator. In such semiparametric models the probability distribution function $P_0$ can be factorized as $P_0(O) = Q_0(O)g_0(O)$, where $g_0$

is the treatment mechanism and $Q_0$ is the relevant factor that defines the g-formula for the counterfactual distributions. The TMLE $\Psi(Q_n^*)$ of $\psi_0 = \Psi(Q_0)$ is consistent if either $Q_n^*$ or $g_n$ is consistent. In our example, $g_n$ is the estimator of the treatment mechanism $g_0(A \mid W) = P_0(A \mid W)$, and $Q_n^*$ is the TMLE of $Q_0$.

## 5.4 Summary

TMLE of a parameter $\Psi(Q_0)$ distinguishes from nonparametric or regularized maximum likelihood estimation by fully utilizing the power of cross-validation (super learning) to fine-tune the bias–variance tradeoff with respect to the part $Q_0$ of the data-generating distribution, thereby increasing adaptivity to the true $Q_0$, and by targeting the fit to remove bias with respect to $\psi_0$. The loss-based super learner of $Q_0$ already outperforms with respect to bias and variance a regularized maximum likelihood estimator for the semiparametric statistical model with respect to estimation of $Q_0$ itself by its asymptotic equivalence to the oracle selector: one could include the regularized maximum likelihood estimator in the collection of algorithms for the super learner. Just due to using the loss-based super learner it already achieves higher rates of convergence for $Q_0$ itself, thereby improving both in bias and variance for $Q_0$ as well as $\Psi(Q_0)$. In addition, due to the targeting step, which again utilizes super learning for estimation of the required $g_0$ in the fluctuation function, it is less biased for $\psi_0$ than the initial loss-function-based super learner estimator, and, as a bonus, the statistical inference based on the central limit theorem is also heavily improved relative to just using a nontargeted regularized maximum likelihood estimator.

Overall it comes down to the following: the TMLE is a semiparametric efficient substitution estimator. This means it fully utilizes all the information in the data (super learning and asymptotic efficiency), in addition to fully using knowledge about global constraints implied by the statistical semiparametric statistical model $\mathcal{M}$ and the target parameter mapping (by being a substitution estimator), thereby making it robust under sparsity with respect to the target parameter. It fully incorporates the power of super learning for the benefit of getting closer to the truth in finite samples.