One-step Targeted Maximum Likelihood for Time-to-event Outcomes

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Abstract

Current targeted maximum likelihood estimation methods used to analyze time to event data estimates the survival probability for each time point separately, which result in estimates that are not necessarily monotone. In this paper, we present an extension of Targeted Maximum Likelihood Estimator (TMLE) for observational time to event data, the one-step Targeted Maximum Likelihood Estimator for the treatment-rule specific survival curve. We construct a one-dimensional universal least favorable submodel that targets the entire survival curve, and thereby requires minimal extra fitting with data to achieve its goal of solving the efficient influence curve equation. Through the use of a simulation study we will show that this method improves on previously proposed methods in both robustness and efficiency, and at the same time respects the monotone decreasing nature of the survival curve.

Key words and phrases: survival analysis, causal effect, causal inference, censored data, cross-validation, one-step targeted maximum likelihood estimation, universal least favorable submodel.

1 Introduction

It is common to want to quantify in observational data the effect of a treatment or exposure on the time it takes for an event to occur. Targeted maximum likelihood estimator (TMLE) method takes an appealing approach by performing fully non-parametric machine-learning estimation, and at the same time doing valid statistical inference on the estimator. Moore and van der Laan (2009) first introduced the TMLE for estimating the treatment-specific survival curve in randomized clinical trials. They showed that the targeted maximum likelihood estimator improves upon common methods for analyzing time to event data in robustness,

efficiency, and interpretability of parameter estimates. Stitelman and van der Laan (2010) extended the estimator using collaborative TMLE (C-TMLE) method to estimate survival curve in observational studies. The C-TMLE methods they developed provide estimates which, in many instances, are more finite sample robust than standard TMLE and all other possible estimation techniques. They also demonstrated that their C-TMLE methodology is able to produce stable estimates of borderline identifiable parameters, when a certain set of baseline covariates are almost completely predictive of a certain treatment within the sample.

Sometimes, we might want to study the entire survival curve instead of survival probability at a single time point. As such, estimators that target the entire survival curve may provide further insight into the mechanism of the treatment. However, existing methodologies are not sufficient when targeting the entire survival curve, an infinite dimensional parameter. Suppose the entire survival curve is characterized by survival probabilities at K distinct time points. The task boils down to estimating a $K-$dimensional target parameter. In the TMLE context, targeting a high-dimensional parameter will result in a submodel with the same number of dimension as the parameter (K). As a result, targeting in all directions simultaneously is not stable and loses the meaning of targeting. A common practice when dealing with high-dimensional target parameters is to separately target each component (Moore and van der Laan, 2009; Stitelman and van der Laan, 2010). However, such an estimator for survival curve ignores the global monotone structure of the curve, potentially generating a non-monotone survival curve.

van der Laan and Gruber (2016) introduced one-step TMLE for which the targeting only takes one step, and thereby requires minimal extra data fitting to achieve its goal of solving the efficient influence curve equation. They developed a one-dimensional universal least favorable submodel such that the one-step TMLE, only minimizing the empirical risk over a univariate parameter, simultaneously solves the multivariate efficient influence curve equation of the target parameter. This allows us to construct a one-step TMLE based on a one-dimensional parametric submodel through the initial estimator, that solves any multivariate desired set of estimating equations. One-step TMLE has already demonstrated good performance on univariate target parameters. van der Laan and Gruber (2016) showed that the one-step TMLE of the "average treatment effect among the treated" parameter is more robust and stable than the iterative TMLE.

In this paper, we construct a one-step TMLE for the treatment-rule specific survival curve, whose empirical score equals the euclidean norm of the vector efficient influence curve equation, so that solving this score equation solves all of them simultaneously. The one-step TMLE reduces variance of the estimate by stabilizing the targeting step, while at the same time always respects the global monotone shape of the survival curve. In addition to

preserving all the asymptotic efficiency of previous TMLE methods, this one-dimensional path provides a "shortest" path towards its high-dimensional goal by pooling information from all parts of the survival curve. We also construct a one-step TMLE estimator for survival at a specific end point, which is the one-step counterpart of the univariate survival probability.

This article is organized as follows. We first outline the data, model and parameter(s) of interest in section 2. We then provide a brief review of iterative targeted maximum likelihood estimation for right-censored survival outcomes in section 3.2. A new application of one-step targeted maximum likelihood estimation to survival probability is presented in section 3.3. In section 3.4 we extend the one-step TMLE estimator to target the entire treatment-rule specific survival curve, followed by its statistical properties and inference. In section 4 we present two simulation studies to demonstrate the efficiency gains of using one-step TMLE over iterative TMLE estimator for survival curves. The performance of the estimators is compared in an application to a real-life dataset in section 5. Finally, we conclude with a discussion in section 6.

2 Data structure & notations

We consider a classic survival analysis data structure with a discrete survival time that is subject to right censoring. We assume that the study consists of n subjects monitored at K equally spaced time points. We focus on the time T it takes for an event to occur which can take values $1, ..., K$. The right-censoring time C is the first time point when the subject is no longer enrolled. We assume T and C are discrete but that by choosing time scale fine enough it also provides methods for continuous survival data. At baseline, each subject is assigned treatment $A \in \{0, 1\}$ and some baseline covariates W are also collected.

We assume the full data is (W, A, T), and we observe a right-censored version of the full data that consists of n i.i.d copies of $O = \left(W, A, \Delta, \widetilde{T}\right) \sim p_0$, where $\widetilde{T} = \min(T, C)$ is the last time point at which the subject is monitored, $\Delta = I(T \leqslant C)$ is the indicator that the subject is not censored and p_0 denotes the probability density of O. This formulation of the data structure is termed the short form of survival data because each row in the data set corresponds to one observed subject (Stitelman and van der Laan, 2010). The same observed study can be equivalently expressed based on counting process. For each unique subject, we define two counting processes, one for the failure event as $N(t) = I\left(\widetilde{T} \leqslant t, \Delta = 1\right)$, and another for the censoring event as $A_c(t) = I\left(\widetilde{T} \leqslant t, \Delta = 0\right)$. $N(t)$ and $A_c(t)$ are indicators of whether the failure or censoring has ever occurred at time t, and both A_c and N become degenerate if one of these processes have jumped to one. We assume time ordering $W, A, N(0), A_c(0), N(1), A_c(1), ..., A_c(K-1), N(K)$, and the observed data is n i.i.d copies

of $O = (W, A, N(t), A_c(t) : t = 0, ..., K) \sim p_0$, where again p_0 denotes the probability density of O.

We denote by P_0 the true probability distribution of O and assume that P_0 falls in some statistical model $\mathcal{M}$. We use the notation $Pf \equiv \int f(o)dP(o)$ for the expectation of f w.r.t. the dominating measure P. We use P_n to denote the empirical measure so that sample averages of f can be written as $P_n f \equiv \sum_{i=1}^{n} f(o_i)$. We take the common notations for the conditional hazards and conditional survival probabilities for both failure and censoring processes. The conditional hazard is defined by

$$\begin{aligned}
\lambda_N(t|A,W) &= P(\tilde{T} = t, \Delta = 1 | \tilde{T} \geqslant t, A, W) && (1)\\
&= P(dN(t) = 1 | N(t-1) = 0, A_c(t-1) = 0, A, W) && (2)\\
\lambda_{A_c}(t|A,W) &= P(\tilde{T} = t, \Delta = 0 | \tilde{T} \geqslant t, A, W) && (3)\\
&= P(dA_c(t) = 1 | N(t) = 0, A_c(t-1) = 0, A, W), && (4)
\end{aligned}$$

where $dN(t) = I\left(\widetilde{T} = t, \Delta = 1\right)$ and $dA_c(t) = I\left(\widetilde{T} = t, \Delta = 0\right)$ are indicators of an observed failure and observed censoring event at time t, respectively. Correspondingly, conditional survival is defined as

$$S_N(t|A,W) = P(T > t|A,W) = \prod_{u=1}^{t} (1 - \lambda_N(u|A,W)) \tag{5}$$

$$S_{A_c}(t|A,W) = P(C > t|A,W) = \prod_{u=1}^{t} (1 - \lambda_{A_c}(u|A,W)), \tag{6}$$

through the product-integral relation between a survival function and a hazard:

$$S(t_0) = \prod_{t=1}^{t_0} (1 - \lambda(t)) \tag{7}$$

Our parameter of interest $\Psi_d(P) = \Psi_d(P)(k), k = 1, ..., K$ is the treatment-rule specific survival curve, where d denotes a dynamic treatment rule, which deterministically maps baseline covariates W to either 0 or 1. $\Psi_d(P)$ is the whole function over time that takes the following form at given k:

$$\begin{aligned}
P \to \Psi_d(P)(k) &= \Psi_d(Q_W, \lambda_N)(k)\\
&= E_{Q_W}\left[S_N\left(k|A = d(W), W\right)\right]\\
&= E_{Q_W}\left[\prod_{t=1}^{k} \left(1 - \lambda_N\left(t|A = d(W), W\right)\right)\right],
\end{aligned} \tag{8}$$

where Q_W is the probability distribution of W and $S_{d,N}(k|W) \triangleq S_N(k|A = d(W), W)$ is the conditional treatment-rule specific survival function of T at k , given W, which is identified by the conditional hazard $\lambda_{d,N}(\cdot|W) \triangleq \lambda_N(\cdot|A = d(W), W)$ through (7). Notice that $\Psi_d(P)(k)$ only depends on P through Q_W, λ_N, therefore we will also denote it with $\Psi_d(Q_W, \lambda_N)(k)$.

We choose the loss function to be negative log-likelihood loss $\mathcal{L}(p)(O) = -\log p(O)$. The density of O under P factorizes as

$$\begin{aligned} p(W, A, N, A_c) = q_W(W) g_A(A|W) \prod_{t \leqslant \widetilde{T}} \lambda_N(t|A, W)^{dN(t)} (1 - \lambda_N(t|A, W))^{1-dN(t)} \\ \prod_{t \leqslant \widetilde{T}} \lambda_{A_c}(t|A, W)^{dA_c(t)} (1 - \lambda_{A_c}(t|A, W))^{1-dA_c(t)}, \end{aligned} \tag{9}$$

where q_W is the density of probability distribution Q_W of W w.r.t. some dominating measure, $g_A(A|W) = P(A|W)$ is the conditional probability of A, given W. We choose the statistical model $\mathcal{M}$ to be nonparametric on the density q_W of W and λ_N and only makes model assumptions on the treatment mechanism $g_{0,A}$ and censoring mechanism λ_{0,A_c}.

If we break up $\Psi_d(P)$ at different time points, the univariate target parameters $P \to \Psi_d(P)(k), k = 1, ..., K$ are pathwise differentiable with canonical gradient (van der Laan and Rubin, 2007; Moore and van der Laan, 2009)

$$\begin{aligned} D^*_{d,k}(P) &= \sum_{t \leqslant k} h_{d,k}(g_{0,A}, S_{0,A_c}, S_{0,N})(t, A, W) \left[I(\widetilde{T} = t, \Delta = 1) - I(\widetilde{T} \geqslant t) \lambda_{0,N}(t|A = d(W), W) \right] \\ &\quad + S_{0,N}(k|A = d(W), W) - \Psi_d(P)(k) \\ &\equiv D^*{}_{1,d,k}(g_{0,A}, S_{0,A_c}, S_{0,N}) + D^*{}_{2,d,k}(P), \end{aligned} \tag{10}$$

where

$$h_{d,k}(g_{0,A}, S_{0,A_c}, S_{0,N})(t, A, W) = -\frac{I(A = d(W))}{g_{0,A}(A = d(W)|W) S_{0,A_c}(t_-|A, W)} \frac{S_{0,N}(k|A, W)}{S_{0,N}(t|A, W)} I(t \leqslant k). \tag{11}$$

3 Methodology

3.1 Targeted Learning in general

The targeted maximum likelihood estimator (TMLE) is an asymptotically efficient substitution estimator obtained by constructing a so called least favorable parametric submodel (LFM) through an initial estimator with score, at zero fluctuation of the initial estimator, that spans the efficient influence curve, and iteratively minimizing the corresponding loss

function till no more updates occur, at which point the updated initial estimator converges and solves the so called efficient influence curve equation

$$P_n D^*(P_n^*) = 0. \tag{12}$$

Thus, the resulting substitution estimator $\Psi(P_n^*)$ inherits the desirable properties of the estimating function based methodology, namely local efficiency and double robustness (Van der Laan and Robins, 2003). TMLE algorithm consists of two steps: 1) initial fit, and 2) targeting. In this paper, we will use the same machine-learning based estimator for the initial fit of the data, and present multiple targeting methods that affects the quality of the final TMLE estimator.

We use a fully non-parametric estimator P_n^0 of all components of the probability distribution P_0. Recall decomposition of likelihood in (9), which is identified by λ_N, λ_{A_c}, g_A, and Q_W. We will estimate $Q_{0,W}$ with the empirical distribution $Q_{n,W}$ of $W_1, ..., W_n$, and we recommend to use SuperLearner (Van der Laan et al., 2007) to estimate the hazard functions for failure and censoring $\lambda_{0,N}$, λ_{0,A_c}, as well as treatment mechanism $g_{0,A}$. SuperLearner for hazard is done by expressing the data by definition of counting process (long form), and then apply a pooled logistic regression on the transformed data format with the loss function being the negative log-likelihood loss (9). For implementation details we refer to Section 8 of Stitelman and van der Laan (2010). A software implementation in R language can be found in Benkeser and Hejazi (2017).

Since we choose the initial empirical distribution for W to estimate Q_W which is the nonparametric maximum likelihood estimate for Q_W and is therefore not updated (Moore and van der Laan, 2009), TMLE will only need to target the estimator of the hazard function $\lambda_{0,N}$ of T, given A, W. The following sections will discuss different targeting submodels to update the hazard of failure process. The current literature presents an iterative TMLE (Moore and van der Laan, 2009; Stitelman and van der Laan, 2010). In this article, we will develop two one-step TMLE, one for survival probability at a specific end point, and one for the entire survival curve.

3.2 Iterative TMLE for survival at a fixed end point

Note that the efficient influence curve for Ψ_d from 1 to K is a K dimensional vector as in (10), therefore solving the efficient influence curve equation,

$$P_n D_d^*(P_n^*) = 0, \tag{13}$$

a K dimensional equation, can be equivalently solved by dividing into K smaller tasks.

$$P_n D_{d,k}^*(P_n^*) = 0, \text{ for all } k = 1, ..., K \tag{14}$$

Each subtask corresponds to independently targeting the treatment-rule specific survival probability at a specific end point $\Psi_d(.)(k), k = 1, ..., K$. Iterative TMLE solves each of the subtask with a corresponding local least favorable submodel (LLFM). The iterative TMLE esimtator for the survival curve is simply connecting the survival probabilities at different end points into a function of time. Iterative TMLE relies on the local least favorable submodel (LLFM) to fluctuate the initial estimator P_n^0. The local least favorable parametric submodel $LLFM(P) = \{P_{n,\varepsilon}^{0,LLFM} : \varepsilon\}$ goes through P_n^0 at $\varepsilon = 0$ with parameter ε and with score $\frac{d}{d\varepsilon} \log \frac{dP_{n,\varepsilon}^{0,LLFM}}{dP_n^0}\Big|_{\varepsilon=0} = D^*(P_n^0)$. We will choose logistic regression fluctuation submodel:

$$\text{logit}\lambda_{n,N}^0(\varepsilon)(t|A,W) = \text{logit}\lambda_{n,N}^0(t|A,W) + \varepsilon h_{d,k,n}(t,A,W), \tag{15}$$

where we define $p(\lambda_{n,N}^0)$ as factor of density only depending on the initial fit $\lambda_{n,N}^0$, ε is the fluctuation parameter of the model and the estimated time-dependent clever covariate $h_{d,k,n}(t,A,W)$ is the same as in (10). We define $\varepsilon_n \triangleq \arg\max_{\varepsilon} \sum_{i=1}^{n} \mathcal{L}(\lambda_{n,N}^0(\varepsilon))(O_i)$, and the targeted maximum likelihood estimation algorithm updates this initial fit by finding ε_n in the updated hazard to maximize the likelihood (9) of the observed data. The update can be done in practice by fitting a univariate logistic regression in the time-dependent covariate $h_{d,k}(t,A,W)$. The coefficient for $\text{logit}\lambda_{n,N}^0(t|A,W)$ is fixed at one and the intercept is set to zero and thus the whole regression is not refitted, rather only ε is estimated. We note in the formulation of the clever covariate (11) that the model can become unstable when the positivity assumption is close to being violated, namely when $g_{0,A}(A = d(W)|W)$ or $S_{0,A_c}(t_-|A,W)$ can be close to zero for some strata of W. This can be stabilized by moving the denominator of (11), $\frac{1}{g_{0,A}(A=d(W)|W)S_{0,A_c}(t_-|A,W)}$, into the weights of the logistic regression.

These steps for evaluating ε_n correspond with a single iteration of the targeted maximum likelihood algorithm. In the second iteration, the updated $\lambda_{n,N}^1(t,A,W)$ now plays the role of the initial fit and the covariate $h_{d,k}(t,A,W)$ is then re-evaluated with the updated $S_{n,N}^1(t|A,W)$ based on $\lambda_{n,N}^1(t,A,W)$. In the third iteration $\lambda_{n,N}^2(t,A,W)$ is fit and the procedure is iterated until ε_n is essentially zero. The final hazard fit at the last iteration of the algorithm is denoted by $\lambda_{n,N}^*(t,A,W)$ with the corresponding survival fit given by $S_{n,N}^*(t|A,W)$. Finally, the targeted maximum likelihood estimates of the probability of surviving past time k for subjects in dynamic treatment arms $d(W)$ given by $\Psi_d(p_0)(k)$ is computed by,

$$\Psi_d(p_n^*)(k) = \frac{1}{n}\sum_{i=1}^{n} S_{n,N}^*(k|A = d(W), W_i).$$

By the fact that the score of the loss equals $D_{d,k}^*$ at $\varepsilon = 0$ it follows that the TMLE p_n^* of p_0 implied by $\lambda_{n,N}^*$ solves the efficient influence curve estimating equation

$$P_n(D_{d,k}^*(g_{n,A}, S_{n,A_c}, \lambda_n^*, Q_{n,W})) = 0, \tag{16}$$

3.3 One-step TMLE for survival at a fixed end point

We define the universal least favorable submodel $ULFM(P)$ as in van der Laan and Gruber (2016). $ULFM(P) = \{P_\varepsilon : \varepsilon \in (-a, a)\} \subset \mathcal{M}$ is a parametric submodel dominated by P, such that $P_{\varepsilon=0} = P$ and for each $\varepsilon \in (-a, a) \subset \mathbb{R}$, we have

$$\frac{d}{d\varepsilon} \log \frac{dP_\varepsilon}{dP} = D^*(P_\varepsilon).$$

We will still use negative log-likeliood loss and SuperLearner initial fit but the submodel is now the universal, instead of local, least favorable submodel. Since the universal least favorable submodel TMLE is one-step, the estimator will not change with any more iteration once the one-step procedure finishes. The universal least favorable submodel succeeds in achieving goal of solving $P_n D^* = 0$ with minimal data fitting. We consider establishing the universal least favorable submodel based on the LLFM for $\lambda_{n,N}$ in the iterative TMLE case in Section 3.2. For $\varepsilon \geqslant 0$ and $d\varepsilon > 0$, we define an increment along the local least favorable model (15) as

$$\text{logit}\lambda_{n,N}^{LLFM}(\varepsilon, d\varepsilon)(t|A, W) = \text{logit}\lambda_{n,N}(\varepsilon)(t|A, W) + d\varepsilon h_{d,k,n}(g_{0,A}, S_{0,A_c}, S_{0,N,\varepsilon}).$$

The universal least favorable submodel can be therefore defined by the following recursive definition:

$$\text{logit}\lambda_{n,N}^{ULFM}(\varepsilon + d\varepsilon)(t|A, W) = \text{logit}\lambda_{n,N}^{LLFM}(\varepsilon, d\varepsilon)(t|A, W). \tag{17}$$

Similarly, we have a recursive relation for $\varepsilon < 0$, but since all these formulas are just symmetric versions of the $\varepsilon > 0$ case, we will focus on $\varepsilon > 0$. This expresses the next $\lambda_{n,N}^{ULFM}(\varepsilon + d\varepsilon)$ in terms of previously calculated $\lambda_{n,N}^{ULFM}(x)$ for $x \leqslant \varepsilon$, thereby fully defining this universal least favorable submodel. This recursive definition (17) corresponds with the following integral representation of this universal least favorable submodel when we take $d\varepsilon \to 0$:

$$\text{logit}\lambda_{n,N}^{ULFM}(\varepsilon)(t|A, W) = \text{logit}\lambda_{n,N}(t|A, W) + \int_0^\varepsilon h_{d,k,n}(g_{0,A}, S_{0,A_c}, S_{0,N,x})dx \tag{18}$$

3.4 One-step TMLE for the whole survival curve

In this section, we will construct a universal least favorable submodel for the whole survival curve. If we would define a multi-dimensional local least favorable submodel, for example using the logistic local least favorable submodel as in section 3.3 but with a multi-dimensional ε, the iterative TMLE would behave poorly after being extended to the multi-dimensional version. In the following section, we construct a universal least favorable submodel by using, for example, the same least favorable submodel, but only maximizing over ε with euclidean

norm smaller than δ or infinitesimal small $d\varepsilon$. Updating, iterating such a model defines a univariate submodel where the small moves of δ represents its parameter. This universal least favorable submodel now has property that the score of the empirical log-likelihood at P equals the euclidean norm of $P_n D^*(P)$, so that one-step TMLE solves all equations simultaneously. The data dependence of the universal least favorable submodel is minimal, only through the empirical mean of components of $D^*(P)$ which are uniformly well-estimated, so that this universal least favorable submodel is much less prone to an overly data adaptive targeting step, only having to maximize over single parameter ε.

Let $\mathcal{H}$ be the Hilbert space of real-valued functions on $\mathbb{R}_{\geqslant 0}$ endowed with inner product ${h_1}^\top h_2 = \langle h_1, h_2 \rangle = \int h_1(t)\, h_2(t)\, d\mu(t)$ for some user-supplied positive and finite measure μ. The norm on this Hilbert space is thus given by $\|h\| = \sqrt{hh^\top} = \sqrt{\int h^2(t)\, d\mu(t)}$. The efficient influence curve for a vector parameter is defined by $D_d^*(P) = ({D^*}_{d,k}(P) : k \geqslant 0)$, where ${D^*}_{d,k}$ takes the definition of (10). Let $q_N(t|A,W)$ be the density of T, given A, W and let $q_{n,N}$ be an initial estimator of this conditional density. For example, one might use machine learning to estimate the conditional hazard $\lambda_{0,N} \equiv q_{0,N}/S_{0,N}$ as in Section 3.1, which then implies a corresponding density estimator $q_{n,N} \equiv \lambda_{n,N} S_{n,N} = \lambda_{n,N}(t|A,W) \prod_{t=1}^{t} (1 - \lambda_{n,N}(t|A,W))$. We are also given an estimator $g_{n,A}$ of $g_{0,A}$, as well as S_{n,A_c} of the censoring probability S_{0,A_c}.

The universal canonical one-dimensional submodel (van der Laan and Gruber, 2016) applied to $q_{n,N}$ is defined by the following recursive relation: for $\varepsilon > 0$,

$$q_{n,N,\varepsilon} = q_{n,N} \exp\left\{ \int_0^\varepsilon \frac{\{P_n {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})\}^\top {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})}{\|P_n {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})\|} dx \right\}$$

To obtain some more insight in this expression, we note, for example, that the inner product is given by:

$$\{P_n {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})\}^\top {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})(O)$$
$$= \int_t P_n {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})\, {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})(O) d\mu(t),$$

and similarly, we have such an integral representation of the norm in the denominator.

Theorem 4 in van der Laan and Gruber (2016), or explicit verification, shows that for all $\varepsilon \geqslant 0$, $q_{n,N,\varepsilon}$ is a conditional density of T, given A, W, and

$$\frac{d}{d\varepsilon} P_n \log q_{n,N,\varepsilon} = \|P_n {D^*}_{1,d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,\varepsilon})\|.$$

Thus, if we move ε away from zero, the log-likelihood increases, and, one searches for the first ε_n so that this derivative is smaller than (for example) $1/n$. Let $q_{n,N}^* = q_{n,N,\varepsilon_n}$, and

$S^*_{n,N,t}(A,W)$ be its corresponding conditional survival function, $t \geqslant 0$. Then our one-step TMLE of the d-specific survival function $\Psi_d(P_0)$ is given by $\Psi^*_{n,d} = \Psi_d\left(Q_{n,W}, S^*_{n,N}\right) = Q_{n,W}S^*_{n,N}$:

$$\Psi^*_{n,d_k}(t) = \frac{1}{n}\sum_{i=1}^{n} S^*_{n,N,t}\left(d(W_i), W_i\right).$$

Since $q^*_{n,N}$ is an actual conditional density, it follows that $\Psi^*_{n,d}$ is a survival function. It has also been shown in van der Laan and Gruber (2016) that the one-step TMLE targeting the whole curve preserves all the asymptotic properties of iterative TMLE method.

3.5 Inference

3.5.1 Point confidence interval

The statistical inference of iterative and one-step TMLE at a single time point can be done in the same procedure. The TMLE estimators, both iterative and one-step, solve the efficient influence curve/score equation:

$$0 = \sum_{i=1}^{n} {D^*}_{d,k}(p^*_n)(O_i)$$

where ${D^*}_{d,k}(p^*_n) = {D^*}_{d,k}(g_{n,A}, S_{n,A_c}, S_{n,N,x})$ is the efficient influence curve presented above in equation (10). Thus, if all components are consistent and under regularity conditions, TMLE is asymptotically linear with influence curve $D^*_{d,k}(p_0)$ (Van der Laan and Robins, 2003). Based on this result, when an estimate $\Psi_d(p^*_n)(k)$ solves the efficient influence curve equation, relying on the consistency of (S^*_N, g_A, S_{A_c}), inference may be based on the empirical variance of the efficient influence curve $D^*_{d,k}(p^*_n)$. Thus, the asymptotic variance of $n^{1/2}\left(\Psi_d(p^*_n)(k) - \Psi_d(p_0)(k)\right)$ is estimated by:

$$\widehat{\sigma}^2 = \frac{1}{n}\sum_{i=1}^{n} {D^*_{d,k}}^2(p^*_n)(O_i).$$

Now a valid $100 \times (1-\alpha)\%$ confidence interval is constructed under the normal distribution in the following way:

$$\Psi_d(p^*_n)(k) \pm q_{1-\alpha/2}\frac{\widehat{\sigma}}{\sqrt{n}},$$

where q_β is the β-quantile of the standard normal distribution.

It has been shown in van der Laan (2012), Moore and van der Laan (2009) and Hubbard et al. (2000) that TMLE has the double robustness property. In the case of estimating treatment-rule specific survival curve, TMLE is asymptotically linear with influence curve equal the efficient influence curve $D^*_{d,k}$ if we consistently estimate S^*_N, g_A, S_{A_c} jointly. If either

S_N^* or the pair g_A, S_{A_c} is consistently estimated, the TMLE is still consistent, and would be asymptotically linear if they are estimated with parametric models. Specifically, if $g_{0,A}, S_{0,A_c}$ are estimated consistently with parametric models or more general models that have a well-behaved MLE (such as cox proportional hazard model), but $S_{n,N}^*$ is possibly inconsistent, then TMLE is still asymptotically linear and the above confidence interval is conservative (Sec 2.5. of Hubbard et al. (2000), and Robins and Rotnitzky (1992)). Either way, we recommend this confidence interval in practice, while using highly adaptive estimators of all the nuisance parameters.

If our parameter of interest is some function of the treatment-rule specific survival estimates, we can apply the δ-method to obtain the estimate of its influence curve. For example, the estimated influence curve for the additive difference in survival at k

$$P_0 \to \Psi_{AD}(p_0)(k) = \Psi_1(p_0)(k) - \Psi_0(p_0)(k) \tag{19}$$

is given by

$$D^*_{d=1,k}(p^*)(O) - D^*_{d=0,k}(p^*)(O),$$

where $D^*_{d=1,k}(p^*)(O)$ and $D^*_{d=0,k}(p^*)(O)$ take the definition as in (10). We can again compute confidence intervals and test statistics for these parameters using the estimated influence curve to estimate the asymptotic variance.

3.5.2 Simultaneous confidence interval

Similar to the construction of point-wise confidence interval, the simultaneous confidence bands for the survival curve estimates can be constructed based on asymptotic linearity of the TMLE. Inference for the survival probabilities ${\Psi^*}_{n,d}$ at K time points, a vector parameter, is also based on the empirical variance of the efficient influence curve D^* itself at the limit of S_N^*, g_A, S_{A_c}. The asymptotic variance of

$$n^{1/2}\left({\Psi^*}_{n,d} - \Psi_d\right)$$

may be consistently estimated by the K by K empirical covariance matrix of the efficient influence curve:

$$\hat{\Sigma} = \frac{1}{n}\sum_{i=1}^{n} D_d^*\left({S_{n,N}}^*, g_{n,A}, S_{n,A_c}\right)(O_i)\left\{D_d^*\left({S_{n,N}}^*, g_{n,A}, S_{n,A_c}\right)(O_i)\right\}^\top.$$

By multivariate central limit theorem, we have

$$n^{1/2}\left({\Psi^*}_{n,d} - \Psi_d\right) \xrightarrow{d} N\left(0, \Sigma_0\right).$$

As a result, an approximate $100 \times (1-\alpha)\%$ simultaneous confidence band is constructed such that for each $\Psi_d(k)$, the k^{th} component of Ψ_d, the region is given by

$$\Psi^*{}_{n,d}(k) \pm q_{1-\alpha}\hat{\Sigma}^{1/2}(k)/\sqrt{n},$$

where $\hat{\Sigma}^{1/2}(k)$ is the (k,k)-th entry in the empirical covariance matrix, thus the empirical variance of $D^*_{d,k}$. $q_{1-\alpha}$ an estimate of the $1-\alpha$ quantile of $\max_t \sqrt{n}\left|\Psi^*{}_{n,d}(t) - \Psi_{0,d}(t)\right| / \widehat{\Sigma}^{1/2}(k)$. Here we need to use that the latter random variable behaves as the max over t of $Z(t)$, where $Z \sim N(0,\rho)$ follows K-dimensional gaussian and ρ is the correlation matrix of the vector influence curve $D^*_{d,k}, k$. We simulate Monte-Carlo samples of Z and calculate $q_{1-\alpha}$ using the empirical $1-\alpha$ quantile of $\max_t |Z|$ of the random samples.

4 Simulation

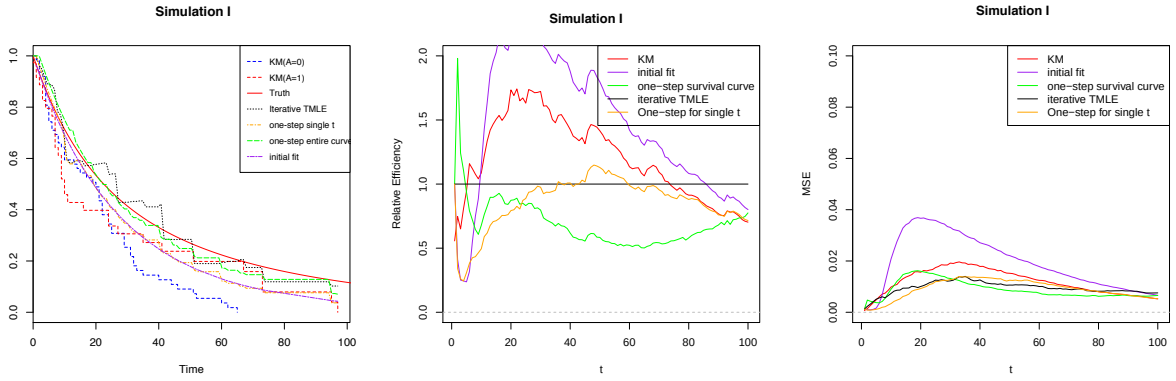
To illustrate some of our proposed methods and explore finite-sample performance, We simulate a continuous baseline covariate W, a binary exposure A, a survival outcome T with censoring time C. We simulate data from the following model so that T, A, and C are confounded by W:

$$\begin{aligned} W &\sim Unif(0, 1.5), \\ A &\sim Bern\left(0.15 + 0.5I\{W > 0.75\}\right), \\ T &\sim \exp\left(\frac{1 + 0.7W^2 - 0.8A}{20}\right), \\ C &\sim Weibull\left(1 - 0.5W, 75\right). \end{aligned}$$

To analyze the above simulated data, we estimated the entire survival curve under the treatment rule that all subjects are treated $\Psi_1(P) = \Psi_1(P)(k), k = 1, ..., K$. Here we implemented the proposed one-step TMLE for the entire survival curve, but also give results for the one-step version for a fixed end point in Section 3.3 and the iterative version in Section 3.2 (with R code for all methods given in 'onestep.survival' package). All estimators depend on estimates of the functions ($\lambda_{0,N}$, λ_{0,A_c}, $g_{0,A}$), which we constructed using identical SuperLearner that contains the correctly specified parametric models. In practice we suggest using more comprehensive learner libraries to minimize the risk of model misspecification. We ran 200 Monte-Carlo simulations of randomized experiments. The Monte-Carlo replications allowed us to estimate the mean squared errors (MSEs) of different estimators. We used the estimated MSEs to further calculate the relative efficiencies (RE) against iterative TMLE for all estimators.

$$RE_{estimator}(k) = \frac{MSE_{estimator}(k)}{MSE_{\text{iterative TMLE}}(k)}, k = 1, ..., K$$

Results for estimating $\Psi_1(P)$ are given in Figure 1.



(a) (b) (c)

Figure 1: (a) one random experiment of two simulation settings. (b) Monte-Carlo results of relative efficiency against iterative TMLE, as a function of t, for sample size 100 and (c) MSE for sample size 300.

The simulation results reflect what is expected based on theory. Figure 1(a) is one experimentation of the data generating distribution. We can tell from the plot that the iterative TMLE is not monotone here, while the one-step TMLE still keeps a monotone decreasing trend. We plot in Figure 1(b) the relative efficiencies at each time point from 0 to 100. Due to confounding of the baseline covariate W, the Kaplan-Meier estimator is biased negatively. The iterative and one-step TMLE are both unbiased, but the iterative TMLE has much larger variance. As a result, the MSE of one-step TMLE for the whole curve can be as small as 50% that of the iterative TMLE. We assess the asymptotic performance of three estimators in Figure 1(c), where we choose the sample sizes to be 300. By plotting the MSEs as a function of time, we see that iterative and one-step TMLE are asymptotically equivalent, while Kaplan-Meier is biased.

5 Data analysis

We apply our proposed methods to an European Union legislation time data studying the effect of a voting procedure on one survival outcome: the legislation being passed. The data consists of 3001 legislations (observations) in EU from 1968 to 1999. At baseline, features about each legislation and its political environment are recorded, and the binary treatment is whether qualified majority vote (QMV) is applied to the legislation (EUR-Lex, 2016). The primary goal of the study was to learn whether the treatment (QMV) affected the time for each legislation to pass. When a legislation takes too long to pass, politicians modify and

start over with a new legislation with a new set of baseline covariates and the old legislation is censored. Golub (2007) give full details of the study population and design.

In our analysis we adjust for all baseline features and QMV, and we used the cross validation-based SuperLearner to combine parametric models (linear for the outcome, logistic for the treatment), generalized additive models, and random forests. Note that the failure event and censoring event are confounded by various factors, therefore non-parametric covariate adjustment should be done for the initial fit of hazard, censoring, and propensity score. We discretized the continuous time into windows of size 30 days,

$$\widetilde{T}' = \lceil \frac{\widetilde{T}}{30} \rceil$$

in order to keep computation tractable. We estimate the treatment-specific survival curves using (i) one-step TMLE for the whole survival curve from section 3.4, (ii) one-step TMLE targeting each time point as in section 3.3, and (iii) iterative TMLE for each time point as in section 3.2. And finally estimate the difference of survival curves as in (19) and compute simultaneous confidence bands for the difference curve from section 3.5.

Results are displayed in figure 2. The survival curves under the treatment arm (red) are uniformly lower than the control arm (blue), no matter what estimator we use. This indicates that the treatment (QMV) reduces the time to pass a legislation, which we defined as the event of interest of the model. Table 1 summarizes the distribution of the denominator of clever covariate (11), $\frac{1}{g_{0,A}(A=d(W)|W)S_{0,A_c}(t_-|A,W)}$, under the counterfactuals $A = 1$ and $A = 0$. There is no extremely large value, suggesting that the positivity assumption holds in this finite sample. The iterative TMLE curve is not monotone, as indicated by the jaggy blue curve between the 15th and 25th 30-day period from Figure 2. On the other hand, the one-step TMLE estimators targeting the entire survival curve or targeting single time points have monotonically decreasing shape. We note that the one-step TMLE targeting the entire survival curve will always guarantee monotonicity under different experiment and data settings.

	Min.	**1st Qu.**	**Median**	**Mean**	**3rd Qu.**	**Max.**
A=1	1.14	1.99	3.71	4.82	6.04	31.30
A=0	1.31	2.34	4.86	10.51	10.58	186.70

Table 1: Empirical distribution of the clever covariate weights $\frac{1}{g_{0,A}(A=d(W)|W)S_{0,A_c}(t_-|A,W)}$, under two counterfactuals $A = 1$ and $A = 0$.

It is natural to also target the difference of the two survival curves (19), which is the causal effect of A on the survival. Figure 3 depicts the estimated difference curve, which draws the same conclusion that QMV has positive effect on accelerating legislation.

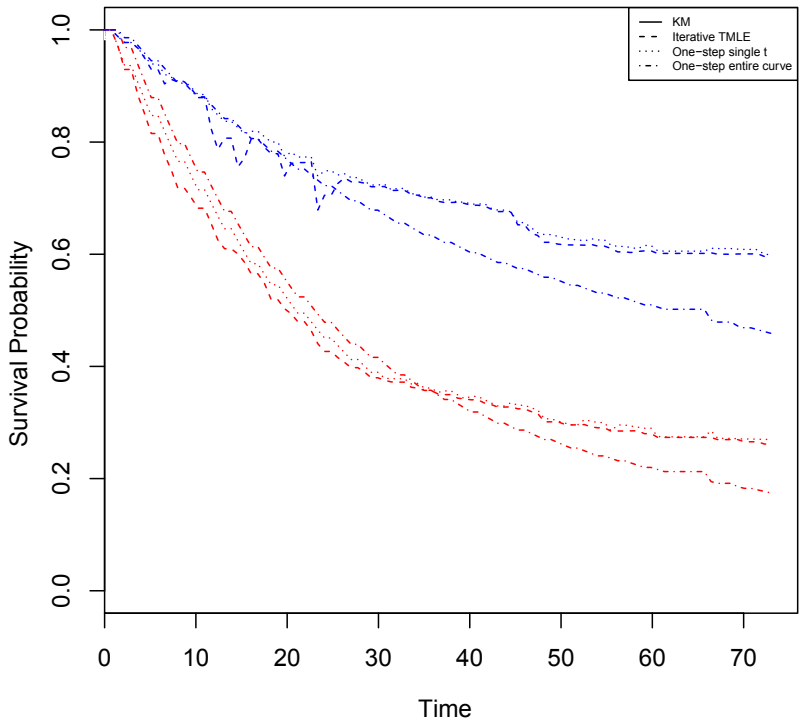


Figure 2: Treatment-rule specific survival curves for interventions QMV = 1 (red) and QMV = 0 (blue) estimated using the Kaplan-Meier, iterative TMLE, one-step TMLE for single time and one-step TMLE targeting entire curve.

6 Discussion

In this paper we provided two one-step TMLE estimators for estimating the treatment-rule specific survival curve: one that targets survival curve at each time separately and another that targets the entire survival curve at once. The one-step estimators have implications for the survival analysis literature by allowing one to construct a TMLE for the infinite dimensional survival curve in a single step. The new methods preserve the asymptotic linearity and efficiency of the iterative TMLE, which adjusts for baseline covariates and accounts for informative censoring through inverse weighting. Additionally, the one-step estimator targeting the entire survival curve respects the monotonically decreasing shape of the estimand. On top of that, the new TMLE for the entire curve also yields a fully compatible TMLE for any function of the whole survival curve, such as median, quantile, or truncated mean. Thus there is no need to compute a new TMLE for each specific feature of the survival curve, or difference of survival curves. All of these advantages come without requiring any parametric modeling assumptions and is robust to misspecification of the hazard fit. Our simulation confirmed the theory in existing literature: that in situations

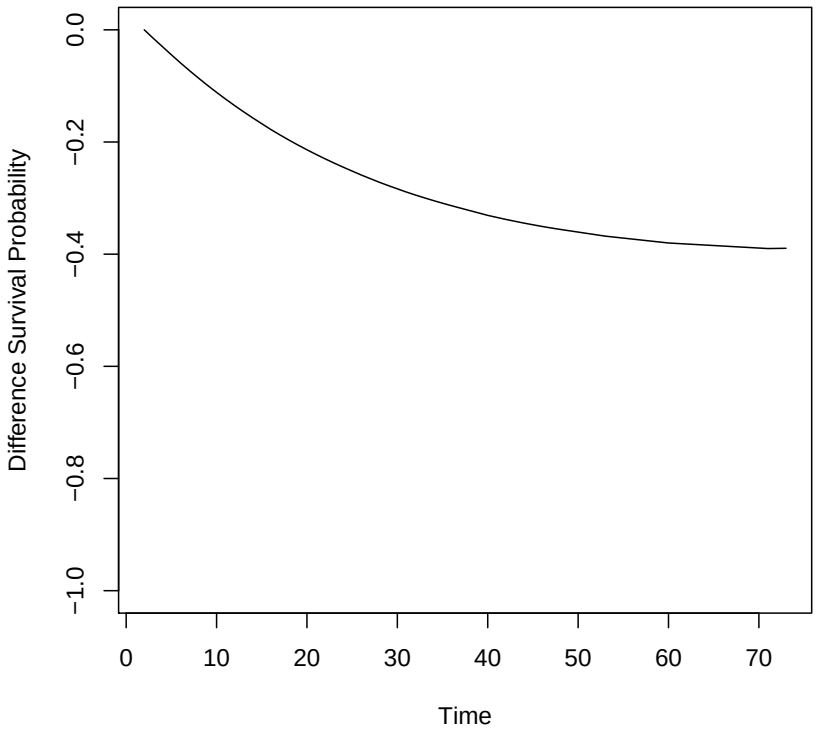


Figure 3: One-step TMLE estimator for the difference of survival curves $\Psi_{AD}(p_0)(k) \triangleq \Psi_1(p_0)(k) - \Psi_0(p_0)(k)$

where targeting is difficult and prone to error, using one-step TMLE that fluctuates universal least favorable submodel may provide robustness and efficiency over iterative TMLE. Under large sample sizes, iterative and one-step TMLE are comparable. We showed that in practical finite sample situations for survival analysis, using universal least favorable submodel to target a multi-dimensional or even infinite-dimensional target parameter is likely to result in a more efficient and stable estimator.

Our paper has shown that using the iterative TMLE targeting the whole curve would not have behaved well at all. So the key is to use the one-step TMLE, which is able to remedy the problem of targeting a high-dimensional target parameter. However, among the two new one-step TMLE estimators that we propose, it is not clear a priori whether targeting one point at a time is worse than targeting the whole curve. Targeting multi-dimensional parameter requires fitting a multi-dimensional logistic regression in the targeting step, which is less stable and more demanding. On the other hand, if the multi-dimensional parameter has high inter-correlation, as is the case in survival curve, pooling the estimators locally can

actually benefit the estimation overall. There is clearly a non-trivial trade-off to be made and our simulations suggest that there is a benefit for targeting the whole curve not just to get a nice monotone curve, but also for achieving a lower mean squared error as well. It is also not clear how our methods compare with doing isotonic regression to the pointwise TMLEs, which is another valid method to consider if getting the whole survival curve is the goal of the analysis.

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Appendix

6.1 Proof that our proposed submodel (18) is a universal least favorable submodel

Let's now explicitly verify that this indeed satisfies the key property of a universal least favorable submodel. Clearly, it is a submodel so that for each ε it yields a hazard, and that it contains $\lambda_{0,N}$ at $\varepsilon = 0$. Recall the loss function (9) evaluated at $\lambda_{n,N}^{ULFM}(\varepsilon)$:

$$\begin{aligned}\mathcal{L}(p_\varepsilon) &= -\log p(\lambda_{n,N}^{ULFM}(\varepsilon)) \\ &\propto -\sum_{t\leqslant k}\left\{dN(t)\log\lambda_{n,N}^{ULFM}(\varepsilon)(t|A,W) + (1-dN(t))\log\left(1-\lambda_{n,N}^{ULFM}(\varepsilon)(t|A,W)\right)\right\}\end{aligned}$$

Use the property of (18) we have

$$\begin{aligned}&\frac{\partial}{\partial\varepsilon}\left\{dN(t)\log\lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W) + (1-dN(t))\log\left(1-\lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W)\right)\right\} \\ &\qquad = -h_{d,k}(g_{0,A},\bar{S}_{0,A_c},S_{0,N}^{ULFM}(\varepsilon))\left[dN(t)-\lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W)\right]\end{aligned}$$

Plug into the loss function, we have the score of $\mathcal{L}(\lambda_{n,N}^{ULFM}(\varepsilon))(O)$ at ε is given by

$$\begin{aligned}
\frac{\partial}{\partial\varepsilon}\mathcal{L}(\lambda_{n,N}^{ULFM}(\varepsilon))(O) &= \sum_{t\leqslant k} h_{d,k}(g_{0,A}, \bar{G}_{0,A_c}, S_{0,N}^{ULFM}(\varepsilon)) \left[dN(t) - \lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W)\right] \\
&= \sum_{t} h_{d,k}\left(g_{0,A}, \bar{G}_{0,A_c}, S_{0,N}^{ULFM}(\varepsilon)\right) \Bigg[I\left(\widetilde{T} = t, \Delta = 1\right) \\
&\qquad - I\left(\widetilde{T} \geqslant t\right) \lambda_{0,N}^{ULFM}(\varepsilon)\left(t|A = d(W), W\right) \Bigg] \\
&= {D^*}_{1,d,k}\left(g_{0,A}, \bar{G}_{0,A_c}, S_{0,N}^{ULFM}(\varepsilon)\right),
\end{aligned}$$

explicitly proving that indeed this is a universal least favorable model for $\lambda_{n,N}$.