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

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Abstract

Current Targeted Maximum Likelihood Estimation (TMLE) methods used to analyze time-to-event data estimate 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 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.

Keywords: survival analysis; survival curve; causal inference; censored data; machine learning; targeted maximum likelihood estimation; high-dimensional data analysis.

1 Introduction

Using machine learning to model time-to-event data extends the application of survival analysis to a wider class of problems beyond the classical medical survival outcome, where factors of the experiment are well controlled. Modern observational time-to-event data analysis flourishes in inter-disciplinary fields such as in radiomics (Leger et al., 2017), device reliability modeling for engineering, and customer lifetime value prediction for online marketing (Wang et al., 2017). A common characteristic of these applications is that there are many high-dimensional, interdependent confounders in the observational data, which demands the
development of flexible, machine learning based methods that can also model time-to-event outcomes. Common methodologies in this topic include survival trees (Gordon and Olshen 1985; Hothorn et al. 2004; LeBlanc and Crowley 1993), survival support vector machines (Khan and Zubek 2008), and deep learning Cox proportional hazard model (Faraggi and Simon 1995). For these existing methods, either there is no statistical efficiency theory result, or the confidence intervals have to be constructed using computationally expensive bootstrap methods.

Targeted maximum likelihood estimator (TMLE) method is an appealing approach by performing fully non-parametric machine-learning estimation, and at the same time obtaining valid statistical inference. Moore and van der Laan (2009) first introduced an iterative TMLE for estimating the treatment-specific survival curve in randomized clinical trials. They showed that the TMLE 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 the survival curve in observational studies, establishing an algorithm for fitting the treatment and censoring mechanism that is targeted towards its utility, namely bias reduction w.r.t. the target estimand of interest. The C-TMLE methods are more robust than standard TMLE in challenging observational settings in which there are many confounders and some of them might act as approximate instrumental variables only affecting the treatment or censoring, while not being predictive of survival (Stitelman and van der Laan 2010). The C-TMLE methodology can also produce stable estimates of borderline identifiable parameters, when a certain set of baseline covariates are almost completely predictive of a particular 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 least favorable submodel with the same dimension as the target parameter ($K$). As a result, simultaneously targeting in all directions is not stable and loses the meaning of targeting in the TMLE procedure. 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 the survival curve ignores the global monotone structure of the curve, potentially generating a non-monotone survival curve (especially for smaller sample sizes or when the survival curve is borderline identifiable).
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. For instance, the one-step TMLE of the “average treatment effect among the treated” parameter is more robust and stable than the iterative TMLE (van der Laan and Gruber, 2016).

In this paper, we construct a one-step TMLE for the treatment-rule specific survival curve, whose empirical score equation equals the Euclidean norm of the empirical mean vector efficient influence curve equation, so that solving this score equation solves all of them simultaneously. The one-step TMLE uses a stable one-dimensional targeting step, while at the same time respecting the global monotone shape of the survival curve. In addition to preserving all the asymptotic efficiency of previous TMLE methods, the 1-dimensional universal least favorable submodel allows an interpretation as a “shortest” path towards its high-dimensional goal of solving the empirical mean of the vector efficient influence curve equation. We also construct a one-step TMLE estimator for survival at a specific endpoint, which is the one-step TMLE counterpart of the iterative TMLE of a 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 to target the entire treatment-rule specific survival curve, establish its statistical properties and provide 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
equally spaced time points. We focus on the time $T$ it takes for an event to occur which can take values $1, \ldots, K$. 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 the 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 pre-treatment baseline covariates $W$ are also collected.

The full data structure on a subject is $(W, A, T)$ with some full-data distribution, and we observe a right-censored version of the full data. That is, our observed data set consists of $n$ i.i.d copies of $O = (W, A, \Delta, \tilde{T}) \sim p_0$, where $\tilde{T} = \min(T, C)$ is the last time point at which the subject is monitored, $\Delta = I(T \leq C)$ 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 data can be equivalently expressed as a right-censored version of the failure and censoring counting processes. For each unique subject, we define two counting processes, one for the failure event as $N(t) = I(\tilde{T} \leq t, \Delta = 1)$, and another for the censoring event as $A_c(t) = I(\tilde{T} \leq t, \Delta = 0)$. $N(t)$ 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 $W, A, N(0), A_c(0), N(1), A_c(1), \ldots, A_c(K - 1), N(K)$, and the observed data is $n$ i.i.d copies of $O = (W, A, N(t), A_c(t) : t = 0, \ldots, K) \sim p_0$, 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 a statistical model $\mathcal{M}$ that only enforces assumptions on the conditional distribution of treatment, given $W$, and on the conditional hazard of censoring, given $A, W$. We use the notation $P f \equiv \int f(o) dP(o)$ for the expectation of $f$ w.r.t. $P$. 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 adopt the common notation for the conditional hazards and conditional survival probabilities for both failure and censoring processes. The conditional hazard is defined by

$$
\lambda_N(t|A, W) = P(\tilde{T} = t, \Delta = 1|\tilde{T} \geq t, A, W) = P(dN(t) = 1|N(t - 1) = 0, A_c(t - 1) = 0, A, W)
$$

$$
\lambda_{A_c}(t|A, W) = P(\tilde{T} = t, \Delta = 0|\tilde{T} \geq t, A, W) = P(dA_c(t) = 1|N(t) = 0, A_c(t - 1) = 0, A, W),
$$

where $dN(t) = I(\tilde{T} = t, \Delta = 1)$ and $dA_c(t) = I(\tilde{T} = t, \Delta = 0)$ are indicators of an observed failure and observed censoring event at time $t$, respectively. Correspondingly, conditional
survival is defined as
\[ S_N(t|A,W) = P(T > t|A,W) = \prod_{u=1}^{t} (1 - \lambda_N(u|A,W)) \]
\[ S_{A_c}(t|A,W) = P(C > t|A,W) = \prod_{u=1}^{t} (1 - \lambda_{A_c}(u|A,W)), \]

through the product-integral relation between a survival function and a hazard:
\[ S(t_0) = t_0 \prod_{t=1}^{t} (1 - \lambda(t)) \quad (1) \]

Our parameter of interest of the data distribution is \( \Psi_d(P) = \Psi_d(P)(k), k = 1, ..., K \), the treatment-rule specific survival curve, where \( d \) denotes a treatment allocation 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 \( k \):
\[ P \rightarrow \Psi_d(P)(k) = \Psi_d(Q_W, \lambda_N)(k) = E_{Q_W}[S_N(k|A = d(W), W)] = E_{Q_W}[\prod_{t=1}^{k} (1 - \lambda_N(t|A = d(W), W))], \]

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 (1). Notice that \( \Psi_d(P)(k) \) only depends on \( P \) through \( Q_W, \lambda_N \), therefore we will also denote it with \( \Psi_d(Q_W, \lambda_N)(k) \).

We choose the loss function of \( P \) to be the negative log-likelihood loss \( L(p)(O) = -\log p(O) \). The density of \( O \) under \( P \) factorizes as
\[ p(W, A, N, A_c) = q_W(W)g_A(A|W) \prod_{t \leq \tilde{T}} \lambda_N(t|A, W) \cdot \lambda_{A_c}(t|A, W) \cdot \lambda_N(t|A, W)^{dN(t)} \cdot (1 - \lambda_{A_c}(t|A, W))^{1-d_{A_c}(t)}, \quad (2) \]

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 \( \lambda_N \) and only potentially make model assumptions on the treatment mechanism \( g_{0,A} \) and censoring mechanism \( \lambda_{0,A_c} \).

If we break up \( \Psi_d(P) \) at different time points, the univariate target parameters \( P \rightarrow \Psi_d(P)(k), k = 1, ..., K \) are pathwise differentiable with canonical gradient (van der Laan and...
\[
D_{d,k}^* (P) = \sum_{t \leq k} h_{d,k}(g_{0,A}, S_{0,A_c}, S_{0,N})(t, A, W) \left[ I(\tilde{T} = t, \Delta = 1) - I(\tilde{T} \geq t) \lambda_{0,N}(t|A = d(W), W) \right] + S_{0,N}(k|A = d(W), W) - \Psi_d(P)(k) \equiv D_{1,d,k}^* (g_{0,A}, S_{0,A_c}, S_{0,N}) + D_{2,d,k}^* (P),
\]

where
\[
h_{d,k}(g_{0,A}, S_{0,A_c}, S_{0,N})(t, A, W) = - \frac{I(A = d(W))I(t \leq k)}{g_{0,A}(A = d(W)|W)S_{0,A_c}(t|A, W)} \frac{S_{0,N}(k|A, W)}{S_{0,N}(t|A, W)}. \tag{4}
\]

3 Methodology

3.1 Targeted Maximum Likelihood Estimator (TMLE) in general

The TMLE is an asymptotically efficient substitution estimator obtained by constructing a so-called least favorable parametric submodel (LFM) through an initial estimator \( P_0 \) of the data distribution. The TMLE has score, at zero fluctuation of the initial estimator, that spans the efficient influence curve at the initial estimator [Van der Laan and Rose 2011]. The TMLE algorithm iteratively minimizes the corresponding empirical loss function (e.g, negative empirical log-likelihood) till no more updates occur, at which point the updated initial estimator \( P_n^* \) has converged, and solves the so-called efficient influence curve equation
\[
P_n D^*(P_n^*) = 0. \tag{5}
\]

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 distribution and present multiple targeting methods that affect the quality of the final TMLE estimator.

We use a fully data-adaptive estimator \( P_n^0 \) of all components of the probability distribution \( P_0 \). Recall the factorization of the likelihood in (2), which is identified by the parameters \( \lambda_N, \lambda_{A_c}, g_A, \) 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 ensemble learning based on cross-validation (i.e, SuperLearner [Van der Laan et al. 2007]) to estimate the conditional hazard functions for failure and censoring \( \lambda_{0,N}, \lambda_{0,A_c} \), as well as treatment mechanism \( g_{0,A} \). Candidate estimators of the conditional hazard are obtained by expressing the data as the longitudinal
data on the counting process (long form), and using one of the many pooled machine learning logistic regressions and parametric logistic regression models, all based on the negative log-likelihood loss \([2]\). Either the estimator with the optimal cross-validated log-likelihood is chosen (discrete super-learner), or the best weighted combination of the candidate estimators is chosen (super-learner) that optimizes the cross-validated log-likelihood over all weighted combinations. For implementation details we refer to Section 8 of \cite{Stitelman2010}. A software implementation in R language can be found in \cite{Benkeser2017}.

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 \cite{Moore2009}, 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 initial estimator of the conditional hazard of failure process. The current literature presents an iterative TMLE \cite{Moore2009, Stitelman2010}. In this article, we will develop two one-step TMLEs, one for survival probability at a specific endpoint, 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 \(\Psi_d\) from 1 to \(K\) is a \(K\) dimensional vector as in \([3]\). One can either construct a \(P^*_n\) that solves the vector equation

\[
P_n D_d^*(P^*_n) = 0,
\]

or, one can construct a separate TMLE \(P^*_{n,k}\) for each \(k = 1, \ldots, K\) solving

\[
P_n D_{d,k}^*(P^*_n) = 0, \quad \text{for all } k = 1, \ldots, K
\]

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

\[
\logit \lambda^0_{n,N}(\varepsilon)(t|A,W) = \logit \lambda^0_{n,N}(t|A,W) + \varepsilon h_{d,k,n}(t,A,W),
\]

7
where we define $p(\lambda_{n,N}^0)$ as factor of density only depending on the initial fit $\lambda_{n,N}^0$, $\varepsilon$ 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 (3). We define $\varepsilon_n \triangleq \arg \max_{\varepsilon} \sum_{i=1}^n L(\lambda_{n,N}^0(\varepsilon))(O_i)$, and the targeting step updates this initial fit by finding $\varepsilon_n$ in the updated hazard to maximize the likelihood (2) 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 $\logit \lambda_{n,N}^0(t|A, W)$ is fixed at one and the intercept is set to zero and thus the whole regression is not refitted, rather only $\varepsilon$ is estimated. We note in the formulation of the clever covariate (4) 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 $S_{0,Ac}(t|A, W)$ can be close to zero for some strata of $W$. This can be stabilized by moving the denominator of (4), $\frac{1}{g_{0,A}(A = d(W)|W)S_{0,Ac}(t|A, W)}$, into the weights for the logistic regression fit, thereby using a weighted log-likelihood loss.

These steps for evaluating $\varepsilon_n$ 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 $\varepsilon_n$ 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 TMLE of the probability of surviving past time $k$ for subjects under the treatment rule $W \rightarrow d(W)$ given by $\Psi_d(p_0)(k)$ is computed by,

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

Here we suppress the dependence of the final TMLE $p_n^*$ on $k$, and we note that $p_n^*$ only involves an update of $\lambda_{n,N}$, while the other factors in $p_n^*$ are equal to their initial estimator values. By the fact that the score of the submodel w.r.t. the log-likelihood loss (or weighted log-likelihood 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 (7):

$$P_n(D_{d,k}^*(g_{n,A}, S_{n,Ac}, \lambda_{n,N}^*, Q_{n,W})) = 0.$$ 

### 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 $\frac{d}{d\varepsilon} \log \frac{dp_0}{dp} = D^*(P_\varepsilon)$. We will still use negative log-likelihood 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 only requires one-step, the estimator will not change with any more iteration once the one-step TMLE is computed. The ULFM succeeds in achieving its goal of solving the vector equation \[6\] with minimal data fitting, as explained in \cite{vanderLaanGruber2016}. We consider establishing the ULFM based on the LLFM for \(\lambda_{n,N}\) in the iterative TMLE case in Section 3.2. For \(\varepsilon \geq 0\) and \(d\varepsilon > 0\), we define an increment along the LLFM \(8\) as

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

The ULFM can be therefore defined by the following recursive definition:

\[
\logit \lambda_{n,N}^{ULFM}(\varepsilon + d\varepsilon)(t|A, W) = \logit \lambda_{n,N}^{LLFM}(\varepsilon, d\varepsilon)(t|A, W).
\] (9)

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 \(x \leq \varepsilon\), thereby fully defining this ULFM. This recursive definition \(9\) corresponds with the following integral representation of this ULFM when we take \(d\varepsilon \to 0\):

\[
\logit \lambda_{n,N}^{ULFM}(\varepsilon)(t|A, W) = \logit \lambda_{n,N}(t|A, W) + \int_0^\varepsilon h_{d,k,n}(g_{0A}, S_{0A}, S_{0N,\varepsilon}) dx
\] (10)

### 3.4 One-step TMLE for the whole survival curve

In this subsection, we construct a ULFM for the whole survival curve. If we would define a multi-dimensional LLFM, for example using the analogue of the 1-dimensional LLFM as in Section 3.3, but with a multi-dimensional \(\varepsilon\) and multidimensional clever covariate \((h_{d,k,n} : k = 1, \ldots, K)\), the iterative TMLE might behave poorly by having to fit a very high dimensional \(\varepsilon\)-parameter. We construct a ULFM by using, for example, the same high-dimensional least favorable submodel, but only maximizing over \(\varepsilon\) with euclidean norm smaller than a small \(\delta\) representing the infinitesimal small \(d\varepsilon\). Iteratively walking along these \(\delta\)-specific fits of the high-dimensional \(\varepsilon\) represents a univariate submodel where the small moves of \(\delta\) represents its parameter, we might denote with \(\varepsilon\) again. This new (data dependent) ULFM through \(P^0_n\) has property that the score of the empirical log-likelihood at \(P^0_{n,\varepsilon}\) equals the euclidean norm of \(P_nD^*(P^0_n)\), so that one-step TMLE solves all equations simultaneously. The data dependence of the ULFM is minimal, only through the empirical mean of components of \(D^*(P)\) which are uniformly well-estimated, so that this ULFM is much less prone to an overly data adaptive targeting step, only having to maximize over single parameter \(\varepsilon\).

Let \(H\) be the Hilbert space of real-valued functions on \(\mathbb{R}_{\geq 0}\) 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 \(\mu\).
The norm on this Hilbert space is thus given by $\|h\| = \sqrt{h^\top h} = \sqrt{\int h^2(t) d\mu(t)}$. The efficient influence curve for a vector parameter is defined by $D_1^*(P) = (D_{d,k}^*(P) : k \geq 0)$, where $D_{d,k}^*$ takes the definition of (3). 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 using the same machine learning method as in Section 3.1, which then implies a corresponding density estimator $q_{n,N}$. 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 $\varepsilon > 0$,

$$q_{n,N,\varepsilon} = q_{n,N} \exp \left\{ \int_0^\varepsilon \frac{P_n D_{1,d,k}^*(g_{n,A}, S_{n,A_{c}}, S_{n,N,x})}{\|P_n D_{1,d,k}^*(g_{n,A}, S_{n,A_{c}}, S_{n,N,x})\|} dx \right\} (11)$$

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

$$\{P_n D_{1,d,k}^*(g_{n,A}, S_{n,A_{c}}, S_{n,N,x})\}^\top D_{1,d,k}^*(O) = \int O^\top P_n D_{1,d,k}^*(g_{n,A}, S_{n,A_{c}}, S_{n,N,x}) d\mu(t),$$

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 $\varepsilon \geq 0$, $q_{n,N,\varepsilon}$ is a conditional density of $T$, given $A,W$, and $\frac{d}{d\varepsilon} P_n \log q_{n,N,\varepsilon} = \|P_n D_{1,d,k}^*(g_{n,A}, S_{n,A_{c}}, S_{n,N,x})\|$. Thus, if we move $\varepsilon$ away from zero, the log-likelihood increases, and, one searches for the first $\varepsilon_n$ so that this derivative is smaller than (for example) $1/n$. Let $q_{n,N}^* = q_{n,N,\varepsilon_n}$, and $S_{n,N,t}^*(A,W), t \geq 0$ be its corresponding conditional survival function. Then our one-step TMLE of the $d$-specific survival function $\Psi_d(P_0)$ is given by $\Psi_{n,d}^* = \Psi_d(Q_{n,W}, S_{n,N}^*) = Q_{n,W} S_{n,N}^*$:

$$\Psi_{n,d}^*(t) = \frac{1}{n} \sum_{i=1}^n S_{n,N,t}^*(d(W_i), W_i).$$

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 equation (3):

$$\sum_{i=1}^n D_{d,k}^*(p_{n}^*)(O_i) = 0$$

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 (3). 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 $\Psi^*(p^*_n)(k)$ solves the efficient influence curve equation, relying on the consistency of $(S_N^*, g_A, S_{Ac})$, inference may be based on the empirical variance of the efficient influence curve $D_{d,k}^*(p^*_n)$. Thus, the asymptotic variance of $n^{1/2}(\Psi^*(p^*_n)(k) - \Psi_d(p_0)(k))$ is estimated by:

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

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

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

where $q_\beta$ is the $\beta$-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 $S_N^*, g_A, S_{Ac}$ jointly. If either $S_N^*$ or the pair $g_A, S_{Ac}$ 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 the 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 $\delta$-method to obtain the estimate of its influence curve. For example, the estimated influence curve for the additive difference in survival at $k$

$$P_0 \rightarrow \Psi_{AD}(p_0)(k) = \Psi_1(p_0)(k) - \Psi_0(p_0)(k)$$

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 (3). 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 uniform in all time points considered. 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 \( S_{N,g}^*, g_{A,S_{A_c}}^* \). The asymptotic variance of \( n^{1/2}(\Psi_{n,d}^* - \Psi_d) \) may be consistently estimated by the \( K \) by \( K \) empirical covariance matrix of the efficient influence curve:

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

By multivariate central limit theorem, we have

\[
n^{1/2}(\Psi_{n,d}^* - \Psi_d) \xrightarrow{d} N(0, \Sigma_0).
\]

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 \( \Psi_d \), 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 \( \max_t \sqrt{n}|\Psi_{n,d}^*(t) - \Psi_{0,d}(t)|/\hat{\Sigma}^{1/2}(k) \).

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 \( \rho \) is the correlation matrix of the vector influence curve \( D_{d,k}^* \). 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. Due to actual weak convergence of the standardized TMLE as a random function in function space endowed with supremum norm, these simultaneous confidence bands are valid even as we take a finer and finer grid of time points as \( n \) increases.

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 \( W \):

\[
W \sim Unif(0, 1.5),
\]

\[
A \sim Bern(0.4 + 0.5I\{W > 0.75\}),
\]

\[
T \sim \text{log-normal}(\mu = 2 - W + A, \sigma = 0.01),
\]

\[
C \sim \text{Weibull}(1 + 0.5W, 75).
\]
To analyze the above simulated data, we estimate the entire survival curve under the treatment rule that all subjects are treated $\Psi_1(P) = \Psi_1(P)(k), k = 1, \ldots, K$. Here we implement the proposed one-step TMLE for the entire survival curve, but also give results for the one-step version for a fixed endpoint in Section 3.3 and the iterative version in Section 3.2 (with R code for all methods given in “MOSS” package (Cai and van der Laan, 2018)). All estimators depend on estimates of the functions $(\lambda_{0,N}, \lambda_{0,A_c}, g_{0,A})$, which we construct 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 run 200 Monte-Carlo simulations of randomized experiments. The Monte-Carlo replications allow us to estimate the mean squared errors (MSEs) of different estimators. We use the MSEs to further calculate the relative efficiencies (RE) against iterative TMLE for all estimators.

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

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

The simulation results reflect what is expected based on theory. Figure (a) is one experimentation of the data generating distribution. We can tell from the plot that the iterative TMLE is not monotone around time $= 16$, while the one-step TMLE still keeps a monotone decreasing trend. We plot in Figure (b) the relative efficiencies at each time point from 0 to 10. Due to the 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 reduced to half that of the iterative TMLE. We assess the asymptotic performance of three estimators in Figure (c), where we choose the sample sizes to be 1000. 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 a European Union legislation time data studying the effect of a voting procedure on one survival outcome: passing the legislation. The data consists of 3001 pieces of legislation (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) affects the time for each legislation to pass. When legislation takes too long to pass, politicians modify and start over with 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 generalized linear models, generalized additive models, and random forests. Note that various factors confound the failure event and censoring event, therefore non-parametric covariate adjustment should be made for the initial fit of survival hazard, censoring hazard, and propensity score. We discretized the continuous time into windows of size 30 days $\tilde{T} = \lceil \frac{T}{30} \rceil$, 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 Equation (12) and compute simultaneous confidence bands for the difference curve from Section 3.5.2.

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.

Figure 2 illustrates the results. 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 legislation, which we defined as the event of interest of the model. Table 1 summarizes the distribution of the clever covariate $\frac{1}{g_0,A(A=d(W)|W)S_0,A_c(t,A,W)}$, 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 for the entire survival curve or for 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 also to target the difference of the two survival curves \([12]\), 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 a positive effect on accelerating legislation.

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

6 Discussion

In this paper, we provided two one-step TMLEs for estimating the treatment-rule specific survival curve: one that targets the 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 the 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 confirms the theory in existing literature: that in situations 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 show 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. It is not clear how our methods compare with applying isotonic regression to the curve defined by the one-step TMLEs targeting one survival probability across all time-points. This represents another valid and possible 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 (10) is a universal least favorable submodel

Clearly, it is a submodel so that for each \( \varepsilon \) it yields a hazard, and that it contains \( \lambda_{0,N} \) at \( \varepsilon = 0 \). Recall the loss function (2) evaluated at \( \lambda_{n,N}^{ULFM}(\varepsilon) \):

\[
\mathcal{L}(p_{\varepsilon}) = -\log p(\lambda_{n,N}^{ULFM}(\varepsilon)) \\
\propto -\sum_{t \leq k} \{dN(t) \log \lambda_{n,N}^{ULFM}(\varepsilon)(t|A,W) + (1 - dN(t)) \log (1 - \lambda_{n,N}^{ULFM}(\varepsilon)(t|A,W))\}
\]

Use the property of (10) we have

\[
\frac{\partial}{\partial \varepsilon} \{dN(t) \log \lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W) + (1 - dN(t)) \log (1 - \lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W))\} \\
= -h_{d,k}(g_{0,A}, \tilde{G}_{0,A,c}, S_{0,N}^{ULFM}(\varepsilon))[dN(t) - \lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W)]
\]

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

\[
\frac{\partial}{\partial \varepsilon} \mathcal{L}(\lambda_{n,N}^{ULFM}(\varepsilon))(O) = \sum_{t \leq k} h_{d,k}(g_{0,A}, \dot{G}_{0,A,c}, S_{0,N}^{ULFM}(\varepsilon))[dN(t) - \lambda_{0,N}^{ULFM}(\varepsilon)(t|A,W)] \\
= \sum_{t} h_{d,k}(g_{0,A}, \dot{G}_{0,A,c}, S_{0,N}^{ULFM}(\varepsilon))\left[I(\tilde{T} = t, \Delta = 1) - I(\tilde{T} \geq t)\lambda_{0,N}^{ULFM}(\varepsilon)(t|A = d(W), W)\right] \\
= D_{1,d,k}(g_{0,A}, \dot{G}_{0,A,c}, S_{0,N}^{ULFM}(\varepsilon)),
\]

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