One-step TMLE for targeting cause-specific absolute risks and survival curves

Tech report

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Abstract

This paper considers one-step targeted maximum likelihood estimation methodology for general competing risks and survival analysis settings where event times take place on the positive real line $\mathbb{R}_+$ and are subject to right-censoring. Our interest is overall in the effects of baseline treatment decisions, static, dynamic or stochastic, possibly confounded by pre-treatment covariates. We point out two overall contributions of our work. First, our method can be used to obtain simultaneous inference across all absolute risks in competing risks settings. Second, we present a practical result for achieving inference for the full survival curve, or a full absolute risk curve, across time by targeting over a fine enough grid of points. The one-step procedure is based on a one-dimensional universal least favorable submodel for each cause-specific hazard that can be implemented in recursive steps along a corresponding universal least favorable submodel. We present a theorem for conditions to achieve weak convergence of the estimator for an infinite-dimensional target parameter. Our empirical study demonstrates the use of the methods.

1 Introduction

This work proceeds on the basis of the work of Laan et al. (2016), van der Laan and Rose (2018, Chapter 5) to construct a one-step targeted maximum likelihood estimation procedure for survival and competing risks settings with event times taking place on the positive real line and interest is in the effect of a treatment assigned at baseline adjusted for baseline covariates. This is the one-step version of the iterative targeted maximum likelihood estimation method presented in Rytgaard et al. (2021b). For the present paper, we point out two important contributions to causal inference in survival and competing risks analysis:

1. We present a method for analyzing treatments effects on all state occupation probabilities in competing risks settings simultaneously. Specifically, our method can be used to achieve multivariate inference across all of the cause-specific absolute risks.

2. Our method provides a practical procedure to obtain weak convergence and asymptotic efficient estimation of the full survival curve, or a cause-specific absolute risk curve, across all time-points in an interval of $\mathbb{R}_+$. 
We emphasize our contribution to competing risks analysis settings. Here, interest is often in the absolute risk, or the subdistribution, of a single event type of interest; however, providing inference solely for a single subdistribution may lead to obscure conclusions like a medical treatment in fact killing patients being a protective treatment for the event of interest. This problem is not solved by considering cause-specific hazard functions instead, as these generally fail to have causal interpretation (Hernán 2010; Martinussen et al. 2018). Alternative one-dimensional causal estimands in competing risks analysis are discussed in recent work by Young et al. (2020) and Stensrud et al. (2020) who propose and distinguish different approaches to isolate effects on a single absolute risks of interest relying on further untestable assumptions on the nature of the treatment mechanism. In our work, we propose an alternative route to carry out a complete analysis of all absolute risks simultaneously; this will reveal all patterns and give the full picture of the effects of a given treatment.

Targeted maximum likelihood estimation (van der Laan and Rubin 2006; van der Laan and Rose 2011) is a general methodology for semiparametric efficient substitution estimation (Bickel et al. 1993; van der Laan and Robins 2003; Tsiatici 2007) of causal parameters consisting of two steps. First, flexible machine learning methods are applied to estimate high-dimensional nuisance parameters. This is followed by a targeting step applied to update the initial estimators to solve a desired equation of interest, the efficient influence curve equation. This second step yields asymptotic linearity, double robustness and efficiency under weak conditions on the statistical model assumed for the data-generating distribution (van der Laan 2017). Our focus in this work is on the targeting step; methods for flexible initial estimation is discussed in previous work, see, e.g., Rytgaard et al. (2021a,b).

The usual targeting procedures are constructed based on local least favorable submodels (van der Vaart 2000; van der Laan and Rose 2011) along which current estimators are updated iteratively to finally solve the efficient score equation of interest. A one-step targeting procedure, on the other hand, is constructed based on universal least favorable submodels, as introduced by Laan et al. (2016), based on which the updating scheme only requires a single iteration. In addition, the universal least favorable submodels provide a method to solve multiple score equation simultaneously, again with only a single update step. As shown by Laan et al. (2016), the maximum likelihood estimator based universal least favorable submodels can be found by recursive infinitesimal updating steps along a local least favorable submodel.

In this work, we construct a one-step targeting procedure to target both multivariate and infinite-dimensional target parameters in survival and competing risks settings. Particularly, we present a methodology for targeting all cause-specific subdistribution simultaneously and for targeting both subdistributions and survival curves across multiple time-points. We further show that we can get inference for the full survival curve across time by targeting over a grid which is fine enough. Due to the simultaneous targeting, the one-step targeted maximum likelihood estimator is guaranteed to yield monotone survival curves and cause-specific absolute risks that are guaranteed to sum up to one, thus completely respecting the parameter space constraints of the problem. Furthermore, the simultaneous inference we provide for the target parameter yields a direct methodology for multiple testing correction. We remark that focus in the current field of semiparametric efficient estimation for survival and competing risks analysis has been on efficient estimation of one-dimensional parameters, corresponding to solving just a single score equation (Hubbard et al. 2000; Moore et al. 2009b; Stitelman et al. 2011a; Benkeser et al. 2018; Ozenne et al. 2020; Rytgaard et al. 2021b). To use these methods to construct efficient estimators for the multivariate target parameters would require separate estimation of each one-dimensional component of the target parameter.

In our one-step procedure, one has the choice between different Hilbert space norms which guide the direction of the one-step targeted update. We consider and discuss three different choices and explore in a simulation study their finite-sample performance compared to each other and to the
iterative targeted maximum likelihood estimation method from Rytgaard et al. (2021b).

2 Setting and notation

We consider a competing risks setting with \( J \geq 1 \) causes with observed data on the form

\[
O = (L, A, \hat{T}, \hat{\Delta}) \in \mathbb{R}^{d'} \times \{0, 1\} \times \mathbb{R}_+ \times \{0, 1, \ldots, J\},
\]

where \( A \in \{0, 1\} \) is a baseline treatment variable, \( L \in \mathbb{R}^{d'} \) are pretreatment covariates, \( \hat{T} \in \mathbb{R}_+ \) is the observed time under observation and \( \hat{\Delta} \in \{0, 1, \ldots, J\} \) is an indicator of right-censoring \( (\hat{\Delta} = 0) \) or type of event \( (\hat{\Delta} \geq 1) \) observed. The variables \( T \in \mathbb{R}_+ \) and \( C \in \mathbb{R}_+ \) represent the times to event, one of \( J \geq 1 \) types, and censoring, respectively, such that the observed time is \( \hat{T} = \min(T, C) \) and \( \hat{\Delta} = 1\{T \geq C\} \Delta \) where \( \Delta \) is the uncensored event indicator. The special-case with \( J = 1 \) corresponds to a classical survival analysis setting.

Let \( P_0 \) denote the distribution of \( O \) and assume that \( P_0 \) belongs to the nonparametric statistical model \( M \). For \( j = 1, \ldots, J \), let \( \lambda_{0,j} \) denote the cause \( j \) specific hazard, defined as

\[
\lambda_{0,j}(t | a, \ell) = \lim_{h \to 0} h^{-1} P(T \leq t + h, \Delta = j | T \geq t, A = a, L = \ell),
\]

and let \( \Lambda_{0,j}(t | a, \ell) \) denote the corresponding cumulative hazard. Likewise, let \( \lambda_0(t | a, \ell) \) denote the conditional hazard for censoring and \( \Lambda_0(t | a, \ell) \) the corresponding cumulative hazard.

Let further \( \mu_0 \) be the density of \( L \) with respect to an appropriate dominating measure \( \nu \) and \( \pi_0(\cdot | L) \) be the conditional distribution of \( A \) given \( L \). The distribution for the observed data can now be represented as \( dP_0(o) = p_0(o) d\nu(\ell) dt \) where \( o = (\ell, a, t, \delta) \) and the density \( p_0 \) under coarsening at random (van der Laan and Robins, 2003) factorizes as follows

\[
p_0(o) = \mu_0(\ell) \pi_0(a | \ell) \left( \lambda_0(t | a, \ell) \right)^{1\{\delta = 0\}} S_0(t- | a, \ell) \prod_{j=1}^J \left( \lambda_{0,j}(t | a, \ell) \right)^{1\{\delta = j\}} S_0(t- | a, \ell); \tag{1}
\]

here, still under coarsening at random,

\[
S_0(t | a, \ell) = \exp \left( - \int_0^t \sum_{j=1}^J \lambda_{0,j}(s | a, \ell) ds \right),
\]

is the survival function and

\[
S_0^c(t | a, \ell) = \exp \left( - \int_0^t \lambda_0^c(s | a, \ell) ds \right),
\]

is the censoring survival function. For \( j = 1, \ldots, J \) we further denote by

\[
F_{0,j}(t | a, \ell) = \int_0^t S_0(s- | a, \ell) \lambda_{0,j}(s | a, \ell) ds,
\]

the absolute risk function, or the subdistribution, for events of type \( j \) (Gray, 1988). We consider the nonparametric statistical model \( M \) such that the density \( p \) of any \( P \in M \) factorizes as in (1).
3 Multivariate target parameters

We start by considering the case where interest is in estimation of a multivariate target parameter taking values in a Hilbert space $\mathcal{H}_{d} \subset \mathbb{R}^d$ endowed with inner product and corresponding norm

$$\langle x, y \rangle_{\Sigma_d} = x^T \Sigma_d^{-1} y, \quad \|x\|_{\Sigma_d} = \sqrt{x^T \Sigma_d^{-1} x},$$

for a user-supplied positive definite matrix $\Sigma_d \in \mathbb{R}^{d \times d}$. Particularly, let now $\Psi : \mathcal{M} \to \mathcal{H}_{d} \subset \mathbb{R}^d$, where $d = JK$, be the multivariate target parameter with components given by

$$\Psi_{j,k}(P) = \mathbb{E}[F_j(t_k | A = a^*, L)] = \mathbb{E}[P(T \leq t_k, \Delta = j \mid A = a^*, L)],$$

for $j = 1, \ldots, J$ and $k = 1, \ldots, K$. Here $a^*$ could be either 1 or 0, to target the treatment or control specific probabilities. Note that taking the difference between the two corresponds to the average treatment effect. Causal assumptions of consistency, positivity and no unmeasured confounding yields a causal interpretation of (3) as the absolute risk of events of type $j$ before time $t_k$ had everyone in the population, possibly contrary to fact, been assigned to treatment level $A = a^*$ (Hernan and Robins, 2020; Rytgaard et al., 2021b). As is well-known, the target parameter in (3) can also be written as

$$\Psi_{j,k}(P) = \int \int F_j(\tau \mid a^*, \ell) \mu(\ell) d\nu(\ell) = \int \int_0^\tau S(s- \mid a^*, \ell) \Lambda_1(ds \mid a^*, \ell) \mu(\ell) d\nu(\ell),$$

seen to depend on all cause-specific hazards via $S(t \mid a^*, \ell) = \exp(-\int_0^t \sum_{j=1}^J \lambda_j(s \mid a^*, \ell) ds)$.

Remark 1 (Euclidean norm) The user-supplied positive definite matrix $\Sigma_d \in \mathbb{R}^{d \times d}$ could be chosen as the identity matrix so that the norm in (2) is simply the standard Euclidean norm. This is the Hilbert space considered and implemented in previously proposed one-step procedures (Laan et al., 2016; Cai et al., 2019). In this work, we will consider other alternative choices of norms as well, see Section 3.4.

3.1 Efficient influence function

The efficient influence function for the $(j,k)$-specific component of the target parameter is given by, see, e.g., Rytgaard et al. (2021b),

$$D_{j,k}^*(P)(O) = \sum_{i=1}^J \int h_{j,i,k,l}(P)(O) \left( N_l(dt) - \mathbb{1} \{ \bar{T} \geq t \} \lambda_l(t \mid A, L) dt \right) + F_j(t_k \mid a, L) - \Psi_{j,k}(P),$$

with the functions $h_{j,i,k,l}$ defined by

$$h_{j,i,k,l}(P)(O) = \frac{1}{\pi(A \mid L)} \sum_{t \leq t_k} \mathbb{1} \{ A = a \} \frac{F_i(t_k \mid A, L) - F_i(t \mid A, L)}{S(t \mid A, L) - S(t \mid A, L)}, \quad \text{when } l = j,$$

characterizing the least favorable paths for the estimation problem. We introduce a vectorized notation and use

$$D^* = (D_{j,k}^* : j = 1, \ldots, J, k = 1, \ldots, K),$$

$$h_{t,t} = (h_{j,i,k,l} : j = 1, \ldots, J, k = 1, \ldots, K),$$
to refer to the $d$-dimensional vector of stacked efficient influence functions and functions indexing the least favorable paths, respectively.

### 3.2 Nuisance parameters for the estimation problem

We note that the target parameter depends only on the cause-specific hazards $\lambda = (\lambda_l : l = 1, \ldots, J)$ and the covariate density $\mu$ whereas the efficient influence function is a mapping $P$ through $\lambda$ and $\mu$ as well as the treatment distribution $\pi$ and the censoring survival function $S^c$. Construction of an efficient estimator requires estimation of all these quantities. To reflect this in our notation we will use the alternative notation

$$\tilde{\Psi}(\lambda) := \Psi(P)$$

when appropriate; note that we have suppressed the dependence on $\mu$ in this notation, as we will simply estimate the average over the covariate distribution by the empirical average. We make the following assumptions on the nuisance parameters.

**Assumption 1 (Conditions on $M$)** Assume that the nuisance parameters $\lambda_1, \ldots, \lambda_J, \lambda^c, \pi$ can be parametrized by functions that are càdlàg (continuous from the right, limits from the left) and have finite sectional variation norm (Gill et al., 1995; van der Laan, 2017). Assume further positivity, i.e., $S^c(\tau | a, L)\pi(a | L) > \kappa > 0$, for $a = 0, 1$, and lastly that $S(\tau | \tilde{A}, L) > \kappa' > 0$.

Assumption 1 particularly allows for the construction of highly adaptive lasso estimators (Benkeser et al., 2016; van der Laan, 2017) for each of the nuisance parameters. For the present paper we simply assume that we have at hand a set of initial estimators $\hat{\lambda}_n, \hat{\pi}_n, \hat{S}^c_n$; for details, see Rytgaard et al. (2021b).

### 3.3 One-step targeted maximum likelihood estimation

To construct the one-step targeted maximum likelihood estimation procedure for the multivariate parameter $\Psi : M \rightarrow A_{\Sigma_d}$, we construct a one-dimensional universal least favorable submodel $\lambda_\varepsilon$ for $\lambda = (\lambda_l : l = 1, \ldots, J)$ such that for any $\varepsilon \geq 0$,

$$\frac{d}{d\varepsilon} \mathbb{P}_n \mathcal{L}(\lambda_\varepsilon) = \| \mathbb{P}_n \tilde{D}^*(\lambda_\varepsilon, \pi, S^c) \|_{\Sigma_d}, \quad (4)$$

for a loss function $(O, \lambda) \mapsto \mathcal{L}(\lambda)(O)$ and fixed $\pi, S^c$.

**Definition 1 (Universal least favorable submodel)** For each cause-specific hazard, we define as follows:

$$\lambda_{l, \varepsilon}(t) = \lambda_l(t) \exp \left( \int_0^\varepsilon \frac{\langle \mathbb{P}_n \tilde{D}^*(\lambda_x, \pi, S^c), \tilde{h}_{l,t}(\lambda_x, \pi, S^c) \rangle_{\Sigma_d} \, dx}{\| \mathbb{P}_n \tilde{D}^*(\lambda_x, \pi, S^c) \|_{\Sigma_d}} \right), \quad l = 1, \ldots, J, \quad (5)$$

and refer to $\lambda_\varepsilon = (\lambda_{l, \varepsilon} : l = 1, \ldots, J)$ as the universal least favorable submodel.

We show that Definition 1 indeed defines a universal least favorable submodel for the log-likelihood loss function. Let $(O, \lambda) \mapsto \mathcal{L}(\lambda)(O)$ denote the sum loss function given as

$$\mathcal{L}(\lambda)(O) = - \sum_{i=1}^J \left( \int_0^T \log \lambda_l(t | A, L) \, N(dt) - \int_0^T 1\{ \tilde{T} \geq t \} \lambda_l(t | A, L) \, dt \right), \quad (6)$$

We show that Definition 1 indeed defines a universal least favorable submodel for the log-likelihood loss function. Let $(O, \lambda) \mapsto \mathcal{L}(\lambda)(O)$ denote the sum loss function given as
For this loss function and the universal least favorable submodel from Definition 1 we have that
\[
\frac{d}{d\varepsilon} \mathcal{L}(\varepsilon) = \left( \frac{P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon)}{\|P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon)\|_{\Sigma_d}} \right) \left( \sum_{j=1}^{J} \int_{0}^{t} \hat{h}_{l,t}(\lambda_\varepsilon, \pi, S^\varepsilon) (N_j(dt) - \lambda_{l,\varepsilon}(t)dt) \right)
\]
\[
= \left( \frac{P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon)}{\|P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon)\|_{\Sigma_d}} \right) P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon) = \|P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon)\|_{\Sigma_d},
\]
which verifies the desired property (4). Particularly, the maximum likelihood estimator along the path defined by the universal least favorable submodel,
\[
\hat{\varepsilon}_n = \arg\min_{\varepsilon \in \mathbb{R}} \mathcal{L}(\varepsilon), \tag{7}
\]
is a local maximum and thus solves \( \|P_n D^*(\lambda_{\hat{\varepsilon}_n}, \pi, S^\varepsilon)\|_{\Sigma_d} = 0 \). It thus follows that \( P_n D^*_{j,t_k}(\lambda_{\hat{\varepsilon}_n}, \pi, S^\varepsilon) = 0 \) for every \( j = 1, \ldots, J \) and \( k = 1, \ldots, K \), i.e., all desired score equations are solved.

### 3.4 Additional steps for implementation

The universal least favorable submodel defined by Equation 5 implies a recursive implementation of the one-step targeting procedure. This follows the practical construction suggested by van der Laan and Rose (2018, Section 5.5.1). Particularly, for each \( l = 1, \ldots, J \), we define as follows
\[
\lambda_{l, dx} = \lambda_l \exp \left( \frac{(P_n \tilde{D}^*(\lambda_\pi, S^\pi))_l \Sigma_d^{-1} \hat{h}_{l,t}(\lambda_\pi, \pi, S^\pi)}{\|P_n D^*(\lambda_\pi, \pi, S^\pi)\|_{\Sigma_d}} \right),
\]
and, for \( m \geq 1 \),
\[
\lambda_{l, (m+1) dx} = \lambda_{l, m dx} \exp \left( \frac{(P_n \tilde{D}^*(\lambda_{mdx}, \pi, S^\pi))_l \Sigma_d^{-1} \hat{h}_{l,t}(\lambda_{mdx}, \pi, S^\pi)}{\|P_n D^*(\lambda_{mdx}, \pi, S^\pi)\|_{\Sigma_d}} \right),
\]
with a small step size \( dx \). The maximum likelihood estimator (7) can now be found by recursively updating any current estimator with the small step size \( dx \). To see why this work, we repeat the arguments of van der Laan and Rose (2018, Section 5.5.1). First note that the universal least favorable submodel (5) can be written as a product integral (Gill and Johansen 1990, Andersen et al. 1993) as follows
\[
\lambda_{l, \varepsilon}(t) = \lambda_l(t) \prod_{0}^{\varepsilon} \left( 1 + \frac{(P_n \tilde{D}^*(\lambda_\varepsilon, \pi, S^\varepsilon))_l \Sigma_d^{-1} \hat{h}_{l,t}(\lambda_\varepsilon, \pi, S^\varepsilon)}{\|P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon)\|_{\Sigma_d}} dx \right), \quad l = 1, \ldots, J,
\]
such that
\[
\lambda^*_{l, \varepsilon}(t) = \lambda_l(t) \prod_{0}^{\varepsilon} \left( 1 + \frac{(P_n \tilde{D}^*(\lambda_\varepsilon, \pi, S^\varepsilon))_l \Sigma_d^{-1} \hat{h}_{l,t}(\lambda_\varepsilon, \pi, S^\varepsilon)}{\|P_n D^*(\lambda_\varepsilon, \pi, S^\varepsilon)\|_{\Sigma_d}} dx \right), \quad l = 1, \ldots, J.
\]
This corresponds (see van der Laan and Rose 2018, Section 5.5.1, p. 66) to a Taylor expansion of a local least favorable submodel \( \lambda_{LFFM}^L \) with
\[
\left( \frac{d}{d\delta} \right)_{\delta=0} \mathcal{L}(\lambda_{LFFM}^L), \delta \right)_{\Sigma_d} = (D^*(P), \delta)_{\Sigma_d}.
We maximize the score locally over \( \delta \) with \( \| \delta \| \leq dx \) using the local least favorable submodel. Maximizing \( \delta \rightarrow \mathbb{P}_n \mathcal{A}(\lambda^*_{S|LM}) \) corresponds to maximizing \( \delta \rightarrow \langle \mathbb{P}_n D^*(P), \delta \rangle_{\Sigma_d} \), which, by the Cauchy-Schwartz inequality, is maximized by

\[
\delta^* = \frac{\mathbb{P}_n D^*(P)}{\| \mathbb{P}_n D^*(P) \|} dx.
\]

Following up on Remark 1, we finish this section proposing the following two other choices for the matrix \( \Sigma_d \in \mathbb{R}^d \times \mathbb{R}^d \) in the definition of the Hilbert space norm.

**Remark 2 (Norm weighted by the variance of the efficient influence function)** Let \( \Sigma_d \in \mathbb{R}^d \times \mathbb{R}^d \) be the diagonal matrix with diagonal values given by the estimated variances \( \hat{\sigma}_{j,k}^2 = \mathbb{P}_n (\hat{D}^*_{j,k}(\lambda_{c_n}, \hat{\pi}_n, \hat{S}_{c_n})^2 \) of the efficient influence functions.

**Remark 3 (Norm weighted by the covariance of the efficient influence function)** Let \( \Sigma_d \in \mathbb{R}^d \times \mathbb{R}^d \) be the empirical covariance matrix \( \Sigma_n = \mathbb{P}_n (\hat{D}^*(\lambda_{c_n}, \hat{\pi}_n, \hat{S}_{c_n})D^*(\lambda_{c_n}, \hat{\pi}_n, \hat{S}_{c_n})^T \) of the stacked efficient influence function \( \hat{D}^*(\lambda_{c_n}, \hat{\pi}_n, \hat{S}_{c_n})^T \).

### 4 Infinite-dimensional target parameters

We now turn our attention to the estimation of infinite-dimensional target parameters \( \Psi : \mathcal{M} \to \mathcal{H} \) with values in a Hilbert space \( \mathcal{H} \) of real-valued functions on \( \mathbb{R}_+ \) endowed with the inner product and corresponding norm

\[
\langle f_1, f_2 \rangle = \int f_1(t)f_2(t)d\Gamma(t), \quad \| f \| = \sqrt{\langle f, f \rangle}
\]

for a user-supplied positive and finite measure \( \Gamma \). We consider particularly the case where \( \Psi(P) \) is the treatment-specific average cause one specific absolute risk curve across time:

\[
\Psi(P)(t) = \mathbb{E}[P(T \leq t, \Delta = 1 \mid A = a^*, L)] = \mathbb{E}[F_1(t \mid A = a^*, L)], \quad t \in [0, \tau]
\]

When there are no competing risks, this is simply one minus the treatment-specific survival curve. As in Section 3.1 we let \( D^*_t(P) \) denote the relevant part of the efficient influence function for \( \Psi(P)(t) \), for \( t \geq 0 \), i.e.,

\[
D^*_t(P)(O) = \sum_{l=1}^J \int_0^\tau h_{1,t,s}(P)(O) \left(N_l(ds) - \mathbb{1}\{T \geq s\} \lambda_l(s \mid A, L)ds\right),
\]

with the functions \( h_{1,t,s}(O) \) for \( l = 1, \ldots, J \) defined by

\[
h_{1,t,s}(P)(O) = \mathbb{1}\{A = a^*\} \mathbb{1}\{s \leq t\} \frac{1 - F_l(t \mid A, L) - F_l(s \mid A, L)}{S_l(s \mid A, L)} - \frac{F_l(t \mid A, L) - F_l(s \mid A, L)}{S_l(s \mid A, L)}, \quad \text{when } l = 1,
\]

\[
h_{1,t,s}(P)(O) = \frac{1 - F_l(t \mid A, L) - F_l(s \mid A, L)}{S_l(s \mid A, L)}, \quad \text{when } l \neq 1.
\]

Again we use the alternative notation \( \hat{\Psi}(\lambda), \hat{D}^*(\lambda, \pi, S^c)(O) \) and \( \hat{h}_{1,t}(\lambda, \pi, S^c) \) when appropriate. The universal least favorable submodel is defined according to Definition 1 with \( \langle \cdot, \cdot \rangle_{\Sigma_d} \) substituted for \( \langle \cdot, \cdot \rangle_{\Sigma_d} \):

\[
\lambda_{l,t}(x) = \lambda_l(t) \exp \left( \int_0^\tau \frac{\langle \mathbb{P}_n \hat{D}^*(\lambda_{c_n}, \pi, S^c), \hat{h}_{l,t}(\lambda_{c_n}, \pi, S^c) \rangle}{\mathbb{P}_n \hat{D}^*(\lambda_{c_n}, \pi, S^c)} dx \right), \quad l = 1, \ldots, J,
\]
such that, together with \( \lambda_\varepsilon = (\lambda_{l,\varepsilon} : l = 1, \ldots, J) \) and the sum loss function \( \mathcal{L} \) from Section 3.3, we have that

\[
 \frac{d}{d\varepsilon} \mathbb{P}_n \mathcal{L}(\lambda_\varepsilon) = \left[ \int \mathbb{P}_n \tilde{D}_t^* (\lambda_\varepsilon, \pi, S) \mathbb{P}_n \left( \sum_{l=1}^J \int \tilde{h}_{l,t} (\lambda_\varepsilon, \pi, S) \left( N_l(dt) - \lambda_{l,\varepsilon}(t) dt \right) \right) d\Gamma(t) \right] / \| \mathbb{P}_n \tilde{D}_t^* (\lambda_\varepsilon, \pi, S) \|.
\]

Remark 4 (Implementation for an infinite-dimensional parameter) As we will see in Section 4.2, the practical construction of the one-step targeting procedure can in fact be carried out along a grid of time-points with a grid that is chosen fine enough. Particularly, this means that the implementation of one-step targeting may follow exactly along that of Section 3.4.

4.1 Conditions for weak convergence

We here review what is needed for simultaneous inference for the infinite-dimensional target parameter. These conditions are also presented in van der Laan and Rose (2018, Chapter 5.6). Let \( \hat{\psi}_n^*(t) = \Psi(\hat{P}_n^*) (t) \) denote an estimator for \( \psi_0(t) = \Psi(P_0)(t) \) and let \( \psi_n^* = (\hat{\psi}_n^*(t) : t \in \mathbb{R}_+) \) as well as \( \psi_0 = (\psi_0(t) : t \in \mathbb{R}_+) \). Further define the second-order remainder \( R_2(\hat{P}_n^*, P_0) = (R_{2,J}(\hat{P}_n^*, P_0) : t \in \mathbb{R}_+) \) by

\[
 R_2(\hat{P}_n^*, P_0) = \hat{\psi}_n^* - \psi_0 + P_0 D^*(\hat{P}_n^*).
\]

Asymptotic linearity and efficiency for \( \hat{\psi}_n^* (t) \) is established for fixed \( j \) and \( k \) by the usual conditions (Rytgaard et al., 2021). The below conditions now tell us what we need for asymptotic efficiency in supremum norm of \( \psi_n^* = \Psi(\hat{P}_n^*) \) in addition to the pointwise efficiency:

(i) The estimator solves the efficient influence curve equation across all time-points, i.e.,

\[
 \sup_{t \in [0, \tau]} \mathbb{P}_n D_t^*(\hat{P}_n^*) = o_P(n^{-1/2}); \quad (10)
\]

(ii) \( \{ D_t^*(P) : P \in \mathcal{M}, t \in \mathbb{R}_+ \} \) is a \( P_0 \)-Donsker class and \( \sup_{t \in [0, \tau]} P_0 \left( D_t^*(\hat{P}_n^*) - D_t^*(P_0) \right)^2 \to 0 \) in probability, and

(iii) \( \sup_{t \in [0, \tau]} | R_{2,J}(\hat{P}_n^*, P_0) | = o_P(n^{-1/2}) \).

Indeed, under conditions (i)–(iii) we have that

\[
 \sqrt{n}(\psi_n^* - \psi_0) = \sqrt{n}(\hat{P}_n - P_0) D^*(P_0) + o_P(1) \xrightarrow{D} \mathcal{C}_0,
\]

where \( \xrightarrow{D} \) denotes convergence in distribution and \( \mathcal{C}_0 \) is a Gaussian process with covariance structure given by the covariance function \( \rho(t_1, t_2) = P_0 D_{t_1}(P_0) D_{t_2}(P_0) \); that is, \( \sqrt{n}(\psi_n^* - \psi_0) \) converges weakly as a random element of the càdlàg function space endowed with the supremum norm to \( \mathcal{C}_0 \).

Remark 5 (Conditions (ii)–(iii)) Conditions (ii) and (iii) are covered by Assumption 7. Indeed, the class of càdlàg functions with finite variation is a well-known Donsker class van der Vaart and Wellner (1996) and since the efficient influence function is a well-behaved mapping of the nuisance parameters, it inherits the Donsker properties. Moreover, Assumption 7 allows for the construction
of highly adaptive lasso estimators \cite{vanDerLaan2017} that have been shown to converge at a rate faster than $n^{-1/3 - \eta}$ with respect to the Kullback-Leibler dissimilarity, for any $\eta > 0$, to the true function \cite{Bibaut2019}. That this is enough to establish (iii) follows from the double robustness structure of the second-order remainder, see \cite{Rytgaard2021} Supplementary Material.

### 4.2 Targeting over a grid to achieve supremum norm inference

In Remark 4 we claimed that we only need to do the targeting over a grid of time-points to solve all score equations, i.e., to solve Equation (10) where $\hat{P}^*_n$ now denotes the one-step targeted estimator. As presented in Section 4.1, weak convergence and asymptotic efficiency in the supremum norm then follows. The claim of Remark 4 follows under the conditions given by the following theorem.

**Theorem 1 (Targeting over a grid)** Define a grid $0 \leq t_1 < t_2 < \cdots < t_{M_n} \leq \tau$ of time-points in $[0, \tau]$ fine enough such that $\max_m (t_m - t_{m-1}) = O_P(n^{-1/3 - \eta})$ for some $\eta > 0$. For each $t \in [0, \tau]$ let $m(t) := \min m | t - t_m |$. Assume, for all $t \in [0, \tau]$ that:

- $A1. \quad P \left( D^*_t (\hat{P}^*_n) - D^*_{m(t)} (\hat{P}^*_n) \right)^2 \overset{P}{\rightarrow} 0$;
- $A2. \quad \| (h_{1, \ell, t_m(t)} - h_{1, \ell, t}) (\hat{P}^*_n) \|_{\mu_0 \otimes \pi_0 \otimes \rho} \leq K |t_m(t) - t|^{1/2}$ for a constant $K > 0$; here, $\| \cdot \|_{\mu_0 \otimes \pi_0 \otimes \rho}$ denotes the $L_2(\mu_0 \otimes \pi_0 \otimes \rho)$-norm where $\rho$ the Lebesgue measure and $\mu_0 \otimes \pi_0 \otimes \rho$ is the product measure of $\mu_0$, $\pi_0$ and $\rho$.

Now, if

$$\max_{t \in \{t_1, \ldots, t_{M_n}\}} P_n D^*_t (\hat{P}^*_n) = o_P(n^{-1/2}),$$

then we have that

$$\sup_{t \in [0, \tau]} P_n D^*_t (\hat{P}^*_n) = o_P(n^{-1/2}).$$

**Proof:** See Appendix A.

**Remark 6 (Assumption A2)** In Appendix B we verify that Assumption A2 holds under a Lipschitz type condition on the cause one subdistribution. We further note that the exponent of $\alpha = 1/2$ for the upper bound $|t_m - t|^\alpha$ of Assumption A2 is specific for our parameter of interest (the absolute risk function). For other choices of target parameters, it may be that $\alpha \in [1/2, 1]$ such that a coarser grid is really needed for weak convergence.

### 4.3 Final remarks on the implementations

We carry out the targeting over the grid $0 \leq t_1 < t_2 < \cdots < t_{M_n} \leq \tau$ according to the procedure outlined in Section 4.2. Particularly, this yields that

$$\| P_n \hat{D}^* (\hat{\lambda}_n, \hat{\pi}_n, \hat{S}_n) \|_{\Sigma_{M_n}} = o_P(n^{-1/2}).$$
where $\| \cdot \|_{\Sigma_{M_n}}$ denotes the grid-$M_n$-dependent Hilbert space norm. To apply Theorem 1, we need to control the maximum norm: Specifically

$$\max_{t \in \{t_1, \ldots, t_{M_n}\}} \frac{\mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)}{\hat{\sigma}_t} \leq \frac{1}{\sqrt{n \log n}},$$

where $\hat{\sigma}_t^2 = \mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)^2$, is enough to ensure (11) of Theorem 1. Lemma 1 below tells us that we can achieve exactly this.

**Lemma 1** Assume that the likelihood is bounded along the path defined by the universal least favorable model:

$$\sup_{\varepsilon \geq 0} \mathbb{P}_n \mathcal{L}(\hat{\lambda}_e) < \infty.$$

Then we can choose $\varepsilon_n^*$ large enough so that for all $\varepsilon \geq \varepsilon_n^*$ we have that

$$\max_{t \in \{t_1, \ldots, t_{M_n}\}} \frac{\mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)}{\sigma_t} \leq \frac{1}{\sqrt{n \log n}}.$$

**Proof:** Assume, for contradiction, that $\lim_{\varepsilon \to \infty} \mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)_{\Sigma_{M_n}} > \eta''$ for some $\eta'' > 0$. Since the likelihood is an increasing function which is bounded and since $\frac{d}{d\varepsilon} \mathbb{P}_n \mathcal{L}(\hat{\lambda}_e) = \|\mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)\|_{\Sigma_{M_n}}$, we reach a contradiction. Thus we have that $\lim_{\varepsilon \to \infty} \mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)_{\Sigma_{M_n}} = 0$, and, accordingly, we can find an $\varepsilon_n^*$ such that for all $\varepsilon \geq \varepsilon_n^*$ we have $\|\mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)\|_{\Sigma_{M_n}} \leq s_n$ for any choice $s_n > 0$. The claim now follows since

$$\max_{t \in \{t_1, \ldots, t_{M_n}\}} \frac{\mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)}{\sigma_t} \leq c_n \|\mathbb{P}_n \tilde{D}_t^*(\hat{\lambda}_e, \hat{\pi}_n, \hat{S}_n^c)\|_{\Sigma_{M_n}},$$

(13)

where $c_n > 0$ is a constant depending on $n$. Thus, if we can control the right hand side of (13), we can control the left hand side.

That the bound (13) holds for the variance-weighted Hilbert space norm proposed in Remark 2 is straightforward. In Appendix C we further demonstrate that it holds for the covariance-weighted norm proposed in Remark 3 with $c_n = \sqrt{M_n}$.

## 5 Empirical study

Our empirical study consists of a demonstration of our proposed methodology on a publicly available dataset and further a simulation study for proof of concept. The purpose is to demonstrate the theoretical properties and to explore the properties of different variations of targeting.

Specifically, we compare throughout the results using the one-step estimator to the iterative counterpart of Rytgaard et al. (2021b) which can be used to target one-dimensional target parameters; thus, to apply this method, we target each component of the particular multivariate target parameter separately.
5.1 Demonstration in a dataset

For a simple demonstration of our methods, we consider the publicly available dataset from the Mayo Clinic trial in primary biliary cholangitis (earlier called primary biliary cirrhosis, or, short, PBC) conducted between 1974 and 1984 as available from the survival package (Therneau, 2020) in R. We also note that an almost identical version of the dataset is described in Fleming and Harrington (2011, Appendix D). The trial included \( n = 312 \) patients who were randomized to treatment with the drug D-penicillamine \((A = 1)\) or to placebo \((A = 0)\). The patients were followed over time until the earliest of liver transplantation \((\Delta = 1)\), death \((\Delta = 2)\) or end of follow-up. In previous analyses, interest was in the effect of the treatment on the risk only of cause one events (liver transplantation), whereas we here consider estimation of the treatment-specific absolute risks of both causes. Our point is solely to demonstrate that our one-step approach leads to a compatible estimator, respecting the bounds of the parameter space, whereas any approach estimating each real-valued component separately is not guaranteed to do so.

We define our target parameter as the vector of treatment-specific absolute risks for both event types across the ten time-points, i.e.,

\[
\Psi(P) = (\Psi_{1,1}(P), \ldots, \Psi_{1,10}(P), \Psi_{2,1}(P), \ldots, \Psi_{2,10}(P)),
\]

with \(\Psi_{1,k}(P) = \mathbb{E}[F_j(t_k \mid A = 1, L)]\) for \(j = 1, 2\) and \(k = 1, \ldots, 10\). Since for all \(t\) we have that \(S(t \mid A, L) = 1 - F_1(t \mid A, L) - F_2(t \mid A, L)\), and thus \(D^*_S,t = -(D^*_1,t + D^*_2,t)\), the one-step targeted estimator which solves the score equations for the two treatment-specific absolute risk functions necessarily solves the score equation for the treatment-specific survival probability too. Table 1 presents the results using the one-step algorithm: As can be noted, the sum of all three estimated state probabilities \((\hat{F}_1 + \hat{F}_2 + \hat{S})\) is ensured to be 1 at all time-points. Table 2 shows the results using the iterative targeting procedure of Rytgaard et al. (2021b) where each treatment-specific probability is targeted on its own leading to incompatible estimators not guaranteed summing up to 1.

| \(t\) | \(t_1\) | \(t_2\) | \(t_3\) | \(t_4\) | \(t_5\) | \(t_6\) | \(t_7\) | \(t_8\) | \(t_9\) | \(t_{10}\) |
|---|---|---|---|---|---|---|---|---|---|---|
| \(\hat{F}_1\) | 0.0000 | 0.0051 | 0.0313 | 0.0317 | 0.0472 | 0.0472 | 0.0557 | 0.0679 | 0.0822 | 0.0822 |
| \(\hat{F}_2\) | 0.0623 | 0.0743 | 0.1157 | 0.1871 | 0.2234 | 0.2741 | 0.3111 | 0.3726 | 0.4183 | 0.4185 |
| \(\hat{S}\) | 0.9377 | 0.9206 | 0.8530 | 0.7812 | 0.7294 | 0.6787 | 0.6332 | 0.5596 | 0.4996 | 0.4993 |
| sum | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 | 1.0000 |

Table 1: Estimated treatment-specific state occupation probabilities using the one-step algorithm for the dataset from the Mayo Clinic trial.

| \(t\) | \(t_1\) | \(t_2\) | \(t_3\) | \(t_4\) | \(t_5\) | \(t_6\) | \(t_7\) | \(t_8\) | \(t_9\) | \(t_{10}\) |
|---|---|---|---|---|---|---|---|---|---|---|
| \(\hat{F}_1\) | 0.0000 | 0.0051 | 0.0305 | 0.0307 | 0.0449 | 0.0449 | 0.0532 | 0.0665 | 0.0821 | 0.0821 |
| \(\hat{F}_2\) | 0.0674 | 0.0792 | 0.1203 | 0.2065 | 0.2443 | 0.2977 | 0.3329 | 0.3969 | 0.4450 | 0.4452 |
| \(\hat{S}\) | 0.9326 | 0.9156 | 0.8489 | 0.7628 | 0.7098 | 0.6574 | 0.6151 | 0.5414 | 0.4811 | 0.4785 |
| sum | 1.0000 | 1.0000 | 0.9997 | 1.0000 | 0.9989 | 0.9999 | 1.0013 | 1.0047 | 1.0082 | 1.0058 |

Table 2: Estimated treatment-specific state occupation probabilities using the iterative algorithm for the dataset from the Mayo Clinic trial.
5.2 Simulation study with survival outcome

For proof of concept, we consider a simulation study with just a single cause of interest. We draw three baseline covariates \( L = (L_1, L_2, L_3) \) such that \( L_1 \) is uniform on \([-1, 1]\) and \( L_2, L_3 \) are uniform on \([0, 1]\). We let treatment be randomized and censoring be covariate independent. The hazard for distribution of the survival time is given as follows

\[
\lambda_1(t \mid A, L) = \lambda_0(t) \exp(-0.15 A + 1.2L_1^2),
\]

with the baseline hazard corresponding to a Weibull distribution. We consider first estimation of a multivariate target parameter, defined as the vector of average treatment effects on the survival curve evaluated across ten pre-specified time-points, i.e.,

\[
\Psi(P) = (\Psi_1(P), \ldots, \Psi_{10}(P)),
\]

with \( \Psi_k(P) = \mathbb{E}[S(t_k \mid A = 1, L) - S(t_k \mid A = 0, L)] \) for \( k = 1, \ldots, 10 \).

To construct the one-step estimator, we repeat the updating steps described in Section 3.4 until

\[
\max_{t \in \{t_1, \ldots, t_{10}\}} \frac{\mathbb{P}_n \hat{D}_t^* (\hat{\lambda}_x^*, \hat{\pi}_n, \hat{S}_n^c)}{\hat{\delta}_t} \leq \frac{1}{\sqrt{n \log n}},
\]

at which point, particularly, \( \mathbb{P}_n \hat{D}_t^* (\hat{\lambda}_x^*, \hat{\pi}_n, \hat{S}_n^c) = o_P(n^{-1/2}) \) for \( k = 1, \ldots, 10 \). The corresponding estimator for the target parameter is \( \hat{\psi}^* = (\hat{\psi}_1^*, \ldots, \hat{\psi}_{10}^*) = (\hat{\Psi}_1(\hat{\lambda}_x^*), \ldots, \hat{\Psi}_{10}(\hat{\lambda}_x^*)) \). Since all efficient score equations are solved simultaneously, asymptotic linearity of the estimators applies across time-points \( t_k \), and we have

\[
\sqrt{n}(\hat{\psi}^* - \psi_0) \xrightarrow{D} N(0, \Sigma_0), \tag{14}
\]

where \( \psi_0 = (\Psi_1(P_0), \ldots, \Psi_{10}(P_0)) \) and \( \Sigma_0 = D^*(P_0)^T D^*(P_0) \in \mathbb{R}^d \times \mathbb{R}^d \) is the covariance matrix of the stacked efficient influence function. Particularly, the asymptotic distribution in (14) can be used to provide simultaneous confidence intervals \( \left( \hat{\psi}_k^* - \hat{q}_{0.95} \hat{\delta}_{t_k} / \sqrt{n}, \hat{\psi}_k^* + \hat{q}_{0.95} \hat{\delta}_{t_k} / \sqrt{n} \right) \) estimates the variance of the \( k \)th efficient influence function, and \( \hat{q}_{0.95} \) is the 95% quantile for the distribution of \( \max_k |\hat{\psi}_k^* - \Psi_k(P_0)|/\sigma_k/\sqrt{n} \). Figure 1 illustrates confidence intervals for a single simulated data set, and further shows the coverage across simulation repetitions of marginal and simultaneous confidence intervals based on the efficient influence function for the \( \sigma_n \)-weighted one-step estimator. Table 3 further shows the relative mean squared error for the \( \sigma_n \)-weighted one-step estimator compared to the unweighted one-step estimator, the \( \Sigma_n \)-weighted one-step estimator, and the iteratively targeted estimator from Rytgaard et al. (2021b).

To further investigate empirically our claim of Theorem 1 we next consider estimation of the treatment-specific survival curve,

\[
\Psi(P)(t) = \mathbb{E}[P(T > t \mid A = 1, L)] = 1 - \mathbb{E}[F(t \mid A = 1, L)],
\]

across \( t \in [0, \tau] \). According to Theorem 1 we only need to solve the efficient influence curve equation over a grid of time-points to solve the efficient influence curve equation across all times \( t \in [0, \tau] \), as long as this grid is chosen fine enough. To check this, we consider targeting over grids of increasing size while checking if we have solved the efficient influence curve equation across 100 randomly sampled time-points. In fact, for practical usage, we suggest that the investigator does the same thing for their data; indeed, one may choose the grid for a particular dataset by increasing the
Table 3: Results from a simulation study with sample size $n = 200$ and $M = 500$ repetitions. Shown are the relative mean squared errors across the $M = 500$ simulation repetitions for the $\sigma_n$-weighted one-step estimator, the $\Sigma_n$-weighted one-step estimator, the unweighted one-step estimator and the iteratively targeted estimator from Rytgaard et al. (2021b) all relative to the $\sigma_n$-weighted one-step estimator.

| $t_k$ | 0.1  | 0.256 | 0.411 | 0.567 | 0.722 | 0.878 | 1.033 | 1.189 | 1.344 | 1.5  |
|-------|------|-------|-------|-------|-------|-------|-------|-------|-------|------|
| $\sigma_n$-weighted | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 | 1.000 |
| $\Sigma_n$-weighted | 1.256 | 1.047 | 1.038 | 1.001 | 1.001 | 1.011 | 1.009 | 1.030 | 1.014 | 1.000 |
| unweighted | 0.980 | 0.997 | 0.993 | 0.981 | 0.982 | 0.990 | 0.989 | 0.988 | 0.986 | 0.976 |
| iterative | 1.254 | 1.045 | 1.016 | 0.995 | 1.004 | 1.011 | 1.008 | 1.025 | 1.024 | 1.014 |

Table 4: Results from targeting over a grid of varying size. The first row shows the grid size used, the second row shows the fraction of the 100 randomly sampled time-points where the efficient influence curve equation is solved and the third row show the maximal ratio of the absolute value standardized empirical mean of the efficient influence curve $|\hat{P}_n D_1^{*}(\hat{\lambda}^*, \hat{\pi}_n, \hat{S}_n^c)|/\hat{\sigma}_t$, across the 100 randomly sampled time-points, relative to the criterion $1/(\sqrt{n \log n})$.

| grid size used: | 20 | 30 | 40 | 60 | 80 | 100 | 120 |
|-----------------|----|----|----|----|----|-----|-----|
| fraction solved: | 0.72 | 0.88 | 0.88 | 0.88 | 0.95 | 0.98 | 0.99 |
| worst-case ratio: | 3.00 | 2.21 | 1.84 | 2.09 | 1.94 | 1.26 | 1.47 |

Table 5 shows the relative mean squared error of estimators for each parameters for the $\sigma_n$-weighted one-step estimator compared to the unweighted one-step estimator, the $\Sigma_n$-weighted one-step estimator, and the iteratively targeted estimator from Rytgaard et al. (2021b). When using the

5.3 Simulation study with competing risks

To investigate the properties of the different choices of Hilbert space norms (see Remarks 1–3) and to further compare with separate estimation via the iteratively targeted estimator from Rytgaard et al. (2021b), we consider here a simulation study with two causes of interest. The two cause-specific hazards are given as follows

$$\lambda_1(t \mid A, L) = \lambda_0(t) \exp(-0.15A + 1.2L_1^2),$$
$$\lambda_2(t \mid A, L) = \lambda_0(t) \exp(0.4 + 0.7L_1 - 0.4A),$$

with the baseline hazard corresponding to a Weibull distribution.

We define now our target parameter as the vector of average treatment effects on the absolute risks across three pre-specified time-points, i.e.,

$$\Psi(P) = (\Psi_{1,1}(P), \Psi_{1,2}(P), \Psi_{1,3}(P), \Psi_{2,1}(P), \Psi_{2,2}(P), \Psi_{2,3}(P)),$$

with $\Psi_{j,k}(P) = \mathbb{E} [F_j(t_k \mid A = 1, L) - F_j(t_k \mid A = 0, L)]$ for $j = 1, 2$ and $k = 1, 2, 3$.

Table 5 shows the relative mean squared error of estimators for each parameters for the $\sigma_n$-weighted one-step estimator compared to the unweighted one-step estimator, the $\Sigma_n$-weighted one-step estimator, and the iteratively targeted estimator from Rytgaard et al. (2021b). When using the
simultaneous coverage = 94.1%

Figure 1: Shown are marginal (black) and simultaneous (gray) 95% confidence intervals based on the efficient influence function for the $\sigma_n$-weighted one-step estimator in a single simulated data set (sample size $n = 200$); above the bars are further shown marginal coverage across the $M = 500$ simulation repetitions. For this dataset, the overall hypothesis that there is no treatment effect on survival across the ten time-points is rejected.

iteratively targeted estimator, we constructed targeted estimators for the average treatment effects on both subdistributions (for each time-point) separately, and computed the effect on the survival probability by summing over the effects on the subdistributions.

| $t_k$ | $\hat{F}_1$ | $\hat{F}_2$ | $\hat{S}$ |
|-------|-------------|-------------|-----------|
| 0.6   | 1.000       | 1.000       | 1.000     |
| 0.8   | 1.000       | 1.047       | 1.001     |
| 1.0   | 1.034       | 1.047       | 1.064     |

Table 5: Results from a simulation study with sample size $n = 200$ and $M = 500$ repetitions. Shown are the relative mean squared errors across the $M = 500$ simulation repetitions for the $\sigma_n$-weighted one-step estimator, the $\Sigma_n$-weighted one-step estimator, the unweighted one-step estimator and the iteratively targeted estimator from Rytgaard et al. (2021b) all relative to the $\sigma_n$-weighted one-step estimator.

6 Concluding remarks

The main contribution of the presented work is the methodology to construct semiparametric efficient plug-in estimators simultaneously targeting all target parameters. As far as we are concerned, there is no other method to achieve this. Another important result is that we can get inference for the full survival curve across time by targeting over a grid which is fine enough; this result is particularly
useful from a practical perspective, allowing for much simpler and faster implementations.

Our simulation studies demonstrate the potential benefits achieved when using our one-step compared to the iterative procedure, both in terms of compatibility (probabilities summing to one, and monotonicity of survival and competing risks curves), but also potentially in terms of finite-sample mean squared error gains. The results of Table 3 and Table 5 give some indications of this.

We further found in our simulations different advantages of the different options for the Hilbert space norm used to construct the one-step targeted update. Indeed, Table 3 shows a slightly lower mean squared error of the unweighted compared to the variance-weighted, whereas Table 5 shows a lower mean squared error of the covariance-weighted compared to the variance-weighted. On the other hand, we generally found the $\Sigma_n$-weighted to converge much faster than both the $\sigma_n$-weighted and the unweighted one-step estimators, and this option may thus be preferred in many situations, especially with larger sample sizes where the mean squared errors gain are diminished. Seemingly, it can differ from one situation to another what is better. This will be investigated further in future work.
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Appendix A

Proof of Theorem [1]

Proof: We consider an expansion as follows:

\[
\mathbb{P}_n D_t^* (\hat{P}_n^*) = \mathbb{P}_n D_t^* (\hat{P}_n^*) - \mathbb{P}_n D_{t_m(t)}^* (\hat{P}_n^*) + o_P(n^{-1/2})
\]

\[
= (\mathbb{P}_n - P_0) (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (\hat{P}_n^*)) + P_0 (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (\hat{P}_n^*)) + o_P(n^{-1/2})
\]

\[
= (\mathbb{P}_n - P_0) (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (\hat{P}_n^*)) + P_0 (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (\hat{P}_n^*)) + o_P(n^{-1/2})
\]

\[
= P_0 (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (\hat{P}_n^*)) - P_0 (D_t^* (P_0) - D_{t_m(t)}^* (P_0))
\]

\[
= P_0 (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (\hat{P}_n^*)) + P_0 (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (P_0))
\]

(\text{(*)})

\[
= f_{n,0}(t) - f_{n,0}(t_m(t)),
\]

note that at the first equality we subtracted \( \mathbb{P}_n D_{t_m(t)}^* (\hat{P}_n^*) \) which is \( o_P(n^{-1/2}) \) per [1], and at the third equality we added \( P_0 D_{t_m(t)}^* (P_0) \) and subtracted \( P_0 D_{t_m(t)}^* (P_0) \) which are both zero. Now, consider (*\text{*) above. By [van der Vaart 2000] Lemma 19.24 and Assumption A1, we have that this is \( o_P(n^{-1/2}) \). Defining \( f_{n,0}(t) := P_0 (D_t^* (\hat{P}_n^*) - D_t^* (P_0)) \), we continue with the remaining terms of (A.15):

\[
P_0 (D_t^* (\hat{P}_n^*) - D_{t_m(t)}^* (\hat{P}_n^*)) - P_0 (D_t^* (P_0) - D_{t_m(t)}^* (P_0))
\]

\[
= f_{n,0}(t) - f_{n,0}(t_m(t)),
\]

where evaluation of \( f_{n,0}(t) \) reveals that

\[
f_{n,0}(t) = \mathbb{E}_P \left[ \sum_{l=1}^{J} \left( \int_{0}^{\tau} h_{l,t,s} (\hat{P}_n^*) (O) (N_{l}(ds) - \mathbb{1} \{ T \geq s \} \lambda_{0,l} (s | A,L) ds) \right. \right.
\]

\[
\left. \left. - \int_{0}^{\tau} h_{l,t,s} (P_0) (O) (N_{l}(ds) - \mathbb{1} \{ T \geq s \} \lambda_{0,l} (s | A,L) ds) \right) \right]
\]

\[
= \mathbb{E}_P \left[ \sum_{l=1}^{J} \int_{0}^{\tau} \left( h_{l,t,s} (\hat{P}_n^*) (O) - h_{l,t,s} (P_0) (O) \right) (N_{l}(ds) - \mathbb{1} \{ T \geq s \} \lambda_{0,l} (s | A,L) ds) \right.
\]

\[
\left. \left. - \sum_{l=1}^{J} \int_{0}^{\tau} h_{l,t,s} (\hat{P}_n^*) (O) (\lambda_{0,l} (s | A,L) - \lambda_{0,l} (s | A,L) ds) \right] \right]
\]

The first line of the right hand side above is a martingale integral of a predictable process; accordingly, this term is simply zero, and we get:

\[
= - \mathbb{E}_P \left[ \sum_{l=1}^{J} \int_{0}^{\tau} h_{l,t,s} (\hat{P}_n^*) (O) (\lambda_{0,l} (s | A,L) - \lambda_{0,l} (s | A,L) ds) \right]
\]

Thus, we have that

\[
f_{n,0}(t) - f_{n,0}(t_m(t))
\]

\[
= \sum_{l=1}^{J} \sum_{a=0,1} \int_{0}^{\tau} \left( h_{l,t,m(t),s} (\hat{P}_n^*) (a,l) (\lambda_{0,l} (s | a,l) - \lambda_{0,l} (s | a,l) ds) \right) \pi_0 (a | l) d\mu_0 (l).
\]
By Assumption A2 we have that the first factor is bounded by $|P_n - P_{\mu_0}^{*\rho}|$. We conclude that $n^{-1/2}$ by the assumption that the grid size goes to zero faster than $n^{-1/3-\eta}$, for some $\eta > 0$. Furthermore, when using the highly adaptive lasso estimator for each cause-specific hazard (Rytgaard et al., 2021b) we have that

$$\|\hat{\lambda}_n^* - \lambda_0\|_{\mu_0 \otimes \pi_0 \otimes \rho} = o_P(n^{-1/3-\eta}).$$

We conclude that $P_n D_n^*(\hat{P}_n) = o_P(n^{-1/2})$ which completes the proof. \qed

**Appendix B**

**On Assumption A2 of Theorem 1**

We here verify that Assumption A2 of Theorem 1 holds for our considered setting under the assumption that

$$\sqrt{\int \sum_{a=0,1} (F_1(t_{m(t)} | a, \ell) - F_1(t | a, \ell))^2 \pi_0(a, \ell) d\mu_0(\ell) \leq K | t_{m(t)} - t |^{1/2}}, \quad (B.17)$$

for a constant $K > 0$. Recall that Assumption A2 states that

$$\|(h_{1,t}, t_{m(t)}(\hat{P}_n^{\ast}))\|_{\mu_0 \otimes \pi_0 \otimes \rho} \leq | t_m - t |^{1/2},$$

where $\| \cdot \|_{\mu_0 \otimes \pi_0 \otimes \rho}$ denotes the $L_2(\mu_0 \otimes \pi_0 \otimes \rho)$-norm, i.e.,

$$\|f\|_{\mu_0 \otimes \pi_0 \otimes \rho} = \sqrt{\int \sum_{a=0,1} \int_0^T (f(t, a, \ell))^2 dt \pi_0(a | \ell) d\mu_0(\ell)}.$$

Let us consider what $(h_{1,t}, t_{m(t)}, s - h_{1,t}, t, s)(P)(A, L)$ looks like:

$$(h_{1,t}, t_{m(t)}, s - h_{1,t}, t, s)(P)(A, L) = \mathbb{I}\{A = a^*\} \frac{1}{\pi(A | L) S^c(s - |A, L)} \begin{cases} \mathbb{I}\{s \leq t_{m(t)}\} \left(1 - \frac{F_1(t_{m(t)} | A, L) - F_1(s | A, L)}{S(s | A, L)} \right) - 1 \{s \leq t\} \left(1 - \frac{F_1(t | A, L) - F_1(s | A, L)}{S(s | A, L)} \right), & \text{when } l = 1, \\ \mathbb{I}\{s \leq t\} \left(\frac{F_1(t | A, L) - F_1(s | A, L)}{S(s | A, L)} \right) - 1 \{s \leq t_{m(t)}\} \left(\frac{F_1(t_{m(t)} | A, L) - F_1(s | A, L)}{S(s | A, L)} \right), & \text{when } l \neq 1. \end{cases}$$
Consider first the case that \( l = 1 \),

\[
\mathbbm{1}\{s \leq t_{m(t)}\} \left( 1 - \frac{F_1(t_{m(t)} \mid A, L) - F_1(s \mid A, L)}{S(s \mid A, L)} \right) - \mathbbm{1}\{s \leq t\} \left( 1 - \frac{F_1(t \mid A, L) - F_1(s \mid A, L)}{S(s \mid A, L)} \right)
\]

\[
= \left( \mathbbm{1}\{s \leq t_{m(t)}\} - \mathbbm{1}\{s \leq t\} \right) \left( 1 + \frac{F_1(s \mid A, L)}{S(s \mid A, L)} \right) - \frac{1}{S(s \mid A, L)} \left( \mathbbm{1}\{s \leq t_{m(t)}\} F_1(t_{m(t)} \mid A, L) - \mathbbm{1}\{s \leq t\} F_1(t \mid A, L) \right).
\]

(B.18)

and then, likewise, the case that \( l \neq 1 \),

\[
\mathbbm{1}\{s \leq t\} \left( \frac{F_1(t \mid A, L) - F_1(s \mid A, L)}{S(s \mid A, L)} \right) - \mathbbm{1}\{s \leq t_{m(t)}\} \left( \frac{F_1(t_{m(t)} \mid A, L) - F_1(s \mid A, L)}{S(s \mid A, L)} \right)
\]

\[
= \left( \mathbbm{1}\{s \leq t_{m(t)}\} - \mathbbm{1}\{s \leq t\} \right) \left( F_1(s \mid A, L) \right) \frac{S(s \mid A, L)}{S(s \mid A, L)} \]

\[
- \frac{1}{S(s \mid A, L)} \left( \mathbbm{1}\{s \leq t_{m(t)}\} F_1(t_{m(t)} \mid A, L) - \mathbbm{1}\{s \leq t\} F_1(t \mid A, L) \right).
\]

(B.19)

Assume with no loss of generality that \( t_{m(t)} \geq t \), and see that

\[
\mathbbm{1}\{s \leq t_{m(t)}\} - \mathbbm{1}\{s \leq t\} = \mathbbm{1}\{s \in (t, t_{m(t)})\}.
\]

Since \( S(t \mid A, L) > \kappa' > 0 \) (Assumption [1]), both expressions in (B.18) and (B.19) are really driven by the term

\[
\mathbbm{1}\{s \leq t_{m(t)}\} F_1(t_{m(t)} \mid A, L) - \mathbbm{1}\{s \leq t\} F_1(t \mid A, L)
\]

\[
= \left( \mathbbm{1}\{s \leq t_{m(t)}\} - \mathbbm{1}\{s \leq t\} \right) F_1(t_{m(t)} \mid A, L) + \mathbbm{1}\{s \leq t\} \left( F_1(t_{m(t)} \mid A, L) - F_1(t \mid A, L) \right)
\]

\[
= \mathbbm{1}\{s \in (t, t_{m(t)})\} F_1(t_{m(t)} \mid A, L) + \mathbbm{1}\{s \leq t\} \left( F_1(t_{m(t)} \mid A, L) - F_1(t \mid A, L) \right). \quad \text{(B.20)}
\]

Collecting what we have above now yields that

\[
(h_{l, t, t_{m(t)}}, s - h_{l, t, t, s})(P)(A, L)
\]

\[
\leq \mathbbm{1}\{A = a^*\} \frac{1}{\pi(A \mid L)} \frac{1}{S^c(s - |A, L|)} \left( \mathbbm{1}\{s \in (t, t_{m(t)})\} \left( 1 + \kappa'^{-1} \right) - \kappa'^{-1} \left( \mathbbm{1}\{s \in (t, t_{m(t)})\} F_1(t_{m(t)} \mid A, L) + \mathbbm{1}\{s \leq t\} \left( F_1(t_{m(t)} \mid A, L) - F_1(t \mid A, L) \right) \right) \right),
\]

\[
\text{(B.21)}
\]
so that,

\[
\| (h_{1,l,t,m} - h_{1,l,t})(\hat{P}_n^*) \|_{\mu_0 \otimes \pi_0 \otimes \rho} \\
\leq \eta \sqrt{\int \sum_{a=0,1} \left( \int_0^T (h_{1,l,t,m(t),s} - h_{1,l,t,s})^2 (\hat{P}_n^*)(s) \pi_0(a | t) d\mu_0(t) \right)} \\
\leq \eta(1 + \kappa')^{1/2} \sqrt{\int \sum_{a=0,1} \left( \int_0^T \mathbb{1}\{s \leq t\} (F_1(t_{m(t)} | a, \ell) - F_1(t | a, \ell))^2 \pi_0(a | \ell) d\mu_0(\ell) \right)} \\
+ \eta \kappa' \left( \int \sum_{a=0,1} \left( \int_0^T \mathbb{1}\{s \leq (t_{m(t)} - t)\} (F_1(t_{m(t)} | a, \ell) - F_1(t | a, \ell))^2 \pi_0(a | \ell) d\mu_0(\ell) \right) \\
+ \eta \kappa' \frac{(t_{m(t)} - t)^{1/2}}{\sqrt{\int \sum_{a=0,1} (F_1(t_{m(t)} | a, \ell) - F_1(t | a, \ell))^2 \pi_0(a | \ell) d\mu_0(\ell)}} \right) \\
\leq \eta(1 + \kappa') \left( t_{m(t)} - t \right) \\
\leq \eta(1 + (2 + K')^{1/2} \left( t_{m(t)} - t \right) \\
\leq \eta(1 + (2 + K')^{1/2} \left( t_{m(t)} - t \right)^{1/2},
\]

by application of the assumption stated in Equation (B.17). This establishes the claim.

**On Assumption A1 of Theorem I**

Under condition (ii) from Section 4.1 we can replace Assumption A1 stating that

\[
P_0 \left( D_t^* (\hat{P}_n^*) - D_{t_{m(t)}}^* (\hat{P}_n^*) \right) = 0,
\]

by:

\[
\sup_t P_0 \left( D_t^* (\hat{P}_n^*) - D_t^* (P_0) \right) 2 \to 0, \quad \text{(B.21)}
\]

\[
\sup_t P_0 \left( D_t^* (P_0) - D_{t_{m(t)}}^* (P_0) \right) 2 \to 0. \quad \text{(B.22)}
\]

This follows since

\[
P_0 \left( D_t^* (\hat{P}_n^*) - D_{t_{m(t)}}^* (\hat{P}_n^*) \right)^2 \\
= P_0 \left( D_t^* (\hat{P}_n^*) - D_t^* (P_0) \right) + D_{t_{m(t)}}^* (P_0) - D_{t_{m(t)}}^* (\hat{P}_n^*) + D_t^* (P_0) - D_{t_{m(t)}}^* (P_0) \right)^2 \\
\leq P_0 \left( D_t^* (\hat{P}_n^*) - D_t^* (P_0) \right)^2 + P_0 \left( D_{t_{m(t)}}^* (P_0) - D_{t_{m(t)}}^* (\hat{P}_n^*) \right)^2 + P_0 \left( D_t^* (P_0) - D_{t_{m(t)}}^* (P_0) \right)^2,
\]

where the second term is \( o_P(n^{-1/2}) \) under condition (ii) from Section 4.1 and the remaining terms are \( o_P(n^{-1/2}) \) by (B.21)–(B.22).
Appendix C

Verifying the bound (13) for the covariance-weighted norm

We demonstrate the bound (13) from Section 4.3 of the main text holds for the covariance-weighted Hilbert space norm proposed in Remark 3. For this purpose, assume that there is at least one \( t_m \) such that \( |\mathbb{P}_n D^*_t (P_x)|/\sigma_{t_m} > c_n \|\mathbb{P}_n D^*(P_x)\|_{M_n} \) where \( c_n = \sqrt{M_n} \). For the positive definite \( M_n \times M_n \) matrix \( \Sigma_{M_n} \) we have that

\[
M_n (\mathbb{P}_n D^*(P_x))^{\top} \Sigma_{M_n}^{-1} \mathbb{P}_n D^*(P_x) \geq (\mathbb{P}_n D^*(P_x))^{\top} D_{M_n}^{-1} \mathbb{P}_n D^*(P_x),
\]

(C.23)

where \( D_{M_n} \) is the diagonal matrix with diagonal equal to the diagonal of \( \Sigma_{M_n} \). Now (C.23) directly implies that

\[
\|\mathbb{P}_n D^*(P_x)\|_{\Sigma_{M_n}} \geq \frac{1}{\sqrt{M_n}} \left( \sum_{m=1}^{M_n} |\mathbb{P}_n D^*_t (P_x)|^2 / \sigma_{t_m}^2 \right) > \|\mathbb{P}_n D^*(P_x)\|_{\Sigma_{M_n}},
\]

contradicting the assumption that \( |\mathbb{P}_n D^*_t (P_x)|/\sigma_{t_m} > c_n \|\mathbb{P}_n D^*(P_x)\|_{M_n} \) with \( c_n = \sqrt{M_n} \) for some \( t_m \). Thus, (13) from Section 4.3 of the main text holds for the covariance-weighted Hilbert space norm with \( c_n = \sqrt{M_n} \).

Verifying (C.23) comes down to showing that \( M_n \Sigma_{M_n}^{-1} - D_{M_n}^{-1} \) is non-negative definite. The matrix \( \Sigma_{M_n} = D_{M_n}^{-1/2} \Sigma_{M_n} D_{M_n}^{-1/2} \) is positive definite with all diagonals elements equal to 1, and we can write \( M_n \Sigma_{M_n}^{-1} - D_{M_n}^{-1} = D_{M_n}^{-1/2} (M_n \Sigma_{M_n}^{-1} - I_{M_n}) D_{M_n}^{-1/2} \) where \( I_{M_n} \) is the \( M_n \times M_n \) identity matrix. The sum of the eigenvalues of \( \Sigma_{M_n} \) equals the trace of \( \Sigma_{M_n} \), which is \( M_n \). Thus, all eigenvalues of \( \Sigma_{M_n} \) belonging to \( (0, n) \) and all eigenvalues of \( \Sigma_{M_n}^{-1} \) belongs to \( (1/n, \infty) \). In conclusion, \( M_n \Sigma_{M_n}^{-1} - I_{M_n} \) is positive definite.

Appendix D

Additional options for implementation

Recall from Section 5.4 that we proceed recursively with small update steps for each \( l \) defining as follows

\[
\hat{\lambda}_{l,mdx} = \lambda_l \exp \left( \left( \frac{\mathbb{P}_n \tilde{D}^* (\hat{\lambda}_m, \hat{\pi}_n, \hat{S}_n^c) \mathbb{P}_n D^*(\lambda_n, \hat{\pi}_n, \hat{S}_n^c)}{\|\mathbb{P}_n \tilde{D}^* (\hat{\lambda}_m, \hat{\pi}_n, \hat{S}_n^c)\|_{\Sigma_d}} \right)^{\top} \Sigma_d^{-1} \mathbb{P}_n D^*(\lambda_n, \hat{\pi}_n, \hat{S}_n^c) \right),
\]

(D.24)

and, for \( m \geq 1 \),

\[
\hat{\lambda}_{l,(m+1)dx} = \lambda_l \hat{\lambda}_{m,mdx} \exp \left( \left( \frac{\mathbb{P}_n \tilde{D}^* (\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c) \mathbb{P}_n D^*(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c)}{\|\mathbb{P}_n \tilde{D}^* (\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c)\|_{\Sigma_d}} \right)^{\top} \Sigma_d^{-1} \mathbb{P}_n D^*(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c) \right);
\]

(D.25)

these recursive update steps are continued until for a given \( m^* \) we have

\[
\max_{j,k} \frac{\mathbb{P}_n \tilde{D}^*_j (\hat{\lambda}_{m^*,dx}, \hat{\pi}_n, \hat{S}_n^c)}{\sigma_{j,k}} \leq \frac{1}{\sqrt{n \log n}},
\]

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However, we also have the option to update along (D.24)–(D.25) only in the directions that have not currently been solved. Recall that

$$P_n\tilde{D}^*(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c) = (P_n\tilde{D}^*_{j,t_k}(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c) : j = 1, \ldots, J, k = 1, \ldots, K)$$.

For a fixed $m$, denote by $J_m, K_m$ the set of indices such that

$$\frac{P_n\tilde{D}^*_{j,t_k}(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c)}{\tilde{\sigma}_{j,k}} \leq \frac{1}{\sqrt{n} \log n}, \quad \text{for } j \in J_m, k \in K_m.$$

Let $0_{J_m,K_m}$ denote the zero vector of length corresponding to the number of elements in $J_m$ and $K_m$. Now, when we update along (D.24)–(D.25), we do not include contributions from $j \in J_m, k \in K_m$; effectively, this means that we substitute the vector

$$((P_n\tilde{D}^*_{j,t_k}(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c), 0_{J_m,K_m}) : j \notin J_m, k \notin K_m)$$

for $P_n\tilde{D}^*(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c)$ in (D.24)–(D.25). At the next round, we likewise define the set of indices $J_{m+1}, K_{m+1}$ such that

$$\frac{P_n\tilde{D}^*_{j,t_k}(\hat{\lambda}_{(m+1)dx}, \hat{\pi}_n, \hat{S}_n^c)}{\tilde{\sigma}_{j,k}} \leq \frac{1}{\sqrt{n} \log n}, \quad \text{for } j \in J_{m+1}, k \in K_{m+1},$$

and use

$$((P_n\tilde{D}^*_{j,t_k}(\hat{\lambda}_{(m+1)dx}, \hat{\pi}_n, \hat{S}_n^c), 0_{J_{m+1},K_{m+1}}) : j \notin J_{m+1}, k \notin K_{m+1}),$$

for updating. Note that there is no guarantee that $J_{m+1} \subseteq J_m$ nor $K_{m+1} \subseteq K_m$, i.e., a particular direction may be solved for a given step but then not solved for later steps. However, we only proceed with a given update step if the norm $\|P_n\tilde{D}^*(\hat{\lambda}_{mdx}, \hat{\pi}_n, \hat{S}_n^c)\|_{\Sigma_d}$ is not increasing from $m$ to $m + 1$; otherwise we decrease the step size and proceed from here. With this approach we repeat the recursive update steps until $J_m^* = \{1, \ldots, J\}$ and $K_m^* = \{1, \ldots, K\}$.