

The state learner

– a super learner for right-censored data

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Abstract

In survival analysis, prediction models are needed as stand-alone tools and in applications of causal inference to estimate nuisance parameters. The super learner is a machine learning algorithm which combines a library of prediction models into a meta learner based on cross-validated loss. Unfortunately, the commonly used partial likelihood loss is not suited for super learning, and inverse probability of censoring weighted loss functions require a pre-specified estimator of the censoring distribution. To relax this, we introduce the state learner, a new super learner for survival analysis, which evaluates the loss based on the observed data simultaneously using libraries of predictions models for the event(s) of interest and the censoring distribution. We establish an oracle inequality for the state learner and investigate its performance through numerical experiments. We illustrate how the state learner allows us to estimate causal effects in a competing risks setting without having to pre-specify models for neither the cause-specific hazards of interest nor the censoring distribution.

1 Introduction

A super learner is a machine learning algorithm that combines a finite set of learners into a meta learner by estimating prediction performance in hold-out samples using a pre-specified loss function [van der Laan et al., 2007]. When the aim is to make a prediction model, super learners typically combine strong learners, such as Cox regression models and random survival forests [Gerds and Kattan, 2021]. While the general idea of combining strong learners based on cross-validation data stems from earlier work [Wolpert, 1992, Breiman, 1996], the name super learner is justified by an oracle inequality [van der Laan and Dudoit, 2003, van der Vaart et al., 2006]: The super learner is guaranteed to perform almost as well as the model which minimizes the expected performance, i.e., the model we would select if we could evaluate the prediction performance in an infinite hold-out sample.

We are concerned with the choice of the loss function for super learning in survival analysis. Existing super learner algorithms for right-censored data use partial log-likelihood loss or inverse probability of censoring weighted loss [Polley and van der Laan, 2011, Keles et al., 2004, Golmakani and Polley, 2020, Westling et al., 2021]. The use of the partial log-likelihood loss restricts the class of learners and excludes for example simple Kaplan-Meier based learners and also more complex random survival forest algorithms. For this reason Golmakani and Polley [2020] restrict their learners to Cox proportional hazard models. A lesser known fact is that a super learner constructed with the negative partial log-likelihood loss implicitly depends on the censoring distribution [Hjort, 1992, Whitney et al., 2019]. A disadvantage of inverse probability of censoring weighted loss functions is that they requires a pre-specified model for the censoring distribution. Westling et al. [2021] tackle this challenge by iterating between super learning of the censoring distribution and the event time distribution.

In this article we define the state learner, a new super learner for right-censored data, which simultaneously evaluates the loss for learners of the event time distribution and the censoring distribution. The loss function which is used to define the state learner is only based on observable quantities. The state learner can be applied to all types of survival estimators, works in the presence of competing risks, and does not require a single pre-specified estimator of the conditional censoring distribution. To analyze the theoretical properties of the state

learner we focus on the so-called discrete super learner which ‘combines’ the library of learners by picking the one that minimizes the cross-validated loss. The state learner uses separate libraries to model each competing event and the censoring distribution. We show that the oracle selector of the state learner is consistent if all libraries contain a consistent learner and prove a finite sample oracle inequality.

The state learner can be used to select a model which predicts the probability of an event based on covariates in the presence of competing risks. Another application is in targeted learning where conditional event probabilities occur as high-dimensional nuisance parameters which need to be estimated at a certain rate [van der Laan and Rose, 2011, Rytgaard et al., 2021, Rytgaard and van der Laan, 2022]. We show how a targeted estimator can be obtained from the state learner, and that a second order product structure for the asymptotic bias term of the targeted estimator is retained when the state learner is used to estimate nuisance parameters.

The article is organized as follows. We introduce our notation and framework in Section 2. In Section 3 we define super learning in general with right-censored data, and in Section 4 we review existing methods. Section 5 introduces our novel proposal, the state learner, and Section 6 provides theoretical guarantees for the state learner. In Section 7 we discuss the use of the state learner in the context of targeted learning. We report some numerical experiments in Section 8 and analyze a prostate cancer data set in Section 9. Section 10 contains a discussion of the merits and limitations of our proposal. Appendices A and B contain proofs.

2 Notation and framework

In a competing risk framework [Andersen et al., 2012], let T be a time to event variable, $D \in \{1, 2\}$ the cause of the event, and $X \in \mathcal{X}$ a vector of baseline covariates taking values in a bounded subset $\mathcal{X} \subset \mathbb{R}^p$, $p \in \mathbb{N}$. Let $\tau < \infty$ be the maximal length of follow-up. We use \mathcal{Q} to denote the collection of all probability measures on $[0, \tau] \times \{1, 2\} \times \mathcal{X}$ such that $(T, D, X) \sim Q$ for some unknown $Q \in \mathcal{Q}$. For $j \in \{1, 2\}$, the cause-specific conditional cumulative hazard functions are defined by $\Lambda_j: [0, \tau] \times \mathcal{X} \rightarrow \mathbb{R}_+$ such that

$$\Lambda_j(t | x) = \int_0^t \frac{Q(T \in ds, D = j | X = x)}{Q(T \geq s | X = x)}.$$

For ease of notation we assume throughout that $\Lambda_j(\cdot | x)$ is continuous for all x and j . We denote by S the conditional event-free survival function,

$$S(t | x) = \exp \{-\Lambda_1(t | x) - \Lambda_2(t | x)\}. \quad (1)$$

Let \mathcal{M} denote the space of all conditional cumulative hazard functions on $[0, \tau] \times \mathcal{X}$. Any distribution $Q \in \mathcal{Q}$ can be characterized by

$$Q(dt, j, dx) = \{S(t- | x)\Lambda_1(dt | x)H(dx)\}^{1_{\{j=1\}}} \\ \{S(t- | x)\Lambda_2(dt | x)H(dx)\}^{1_{\{j=2\}}},$$

where $\Lambda_j \in \mathcal{M}$ for $j = 1, 2$ and H is the marginal distribution of the covariates.

We consider the usual right-censored setting in which we observe data $O = (\tilde{T}, \tilde{D}, X)$, where $\tilde{T} = \min(T, C)$ for a right-censoring time C , $\Delta = \mathbb{1}\{T \leq C\}$, and $\tilde{D} = \Delta D$. Let \mathcal{P} denote a set of probability measures on the sample space $\mathcal{O} = [0, \tau] \times \{0, 1, 2\} \times \mathcal{X}$ such that $O \sim P$ for some unknown $P \in \mathcal{P}$. We assume that the event time and the censoring

time are conditionally independent given covariates, $T \perp\!\!\!\perp C \mid X$. This implies that any distribution $P \in \mathcal{P}$ is characterized by a distribution $Q \in \mathcal{Q}$ and a conditional cumulative hazard function for C given X [c.f., Begun et al., 1983, Gill et al., 1997]. We use $\Gamma \in \mathcal{M}$ to denote the conditional cumulative hazard function for censoring. We assume that $\Gamma(\cdot \mid x)$ is continuous for all x , and let $G(t \mid x) = \exp \{-\Gamma(t \mid x)\}$ denote the survival function of the conditional censoring distribution. In our setting with competing risks, this yields

$$\begin{aligned} P(dt, j, dx) &= \{G(t- \mid x)S(t- \mid x)\Lambda_1(dt \mid x)H(dx)\}^{\mathbb{1}\{j=1\}} \\ &\quad \{G(t- \mid x)S(t- \mid x)\Lambda_2(dt \mid x)H(dx)\}^{\mathbb{1}\{j=2\}} \\ &\quad \{G(t- \mid x)S(t- \mid x)\Gamma(dt \mid x)H(dx)\}^{\mathbb{1}\{j=0\}} \\ &= \{G(t- \mid x)Q(dt, j, dx)\}^{\mathbb{1}\{j \neq 0\}} \\ &\quad \{G(t- \mid x)S(t- \mid x)\Gamma(dt \mid x)H(dx)\}^{\mathbb{1}\{j=0\}}. \end{aligned} \quad (2)$$

Hence, we may write $\mathcal{P} = \{P_{Q,\Gamma} : Q \in \mathcal{Q}, \Gamma \in \mathcal{G}\}$ for some $\mathcal{G} \subset \mathcal{M}$. We also have

$$P(\tilde{T} > t \mid X = x) = S(t \mid x)G(t \mid x) = \exp \{-\Lambda_1(t \mid x) - \Lambda_2(t \mid x) - \Gamma(t \mid x)\}.$$

We further assume that there exists $\kappa < \infty$ such that $\Lambda_j(\tau- \mid x) < \kappa$, for $j \in \{1, 2\}$, and $\Gamma(\tau- \mid x) < \kappa$ for almost all $x \in \mathcal{X}$. Note that this implies that $G(\tau- \mid x)$ is bounded away from zero for almost all $x \in \mathcal{X}$. Under these assumptions, the conditional cumulative hazard functions Λ_j and Γ can be identified from P by

$$\Lambda_j(t \mid x) = \int_0^t \frac{P(\tilde{T} \in ds, \tilde{D} = j \mid X = x)}{P(\tilde{T} \geq s \mid X = x)}, \quad (3)$$

$$\Gamma(t \mid x) = \int_0^t \frac{P(\tilde{T} \in ds, \tilde{D} = 0 \mid X = x)}{P(\tilde{T} \geq s \mid X = x)}. \quad (4)$$

Thus, we can consider Λ_j and Γ as operators which map from \mathcal{P} to \mathcal{M} .

3 Super learning with right-censored survival data

A super learner estimates a parameter Ψ which can be identified from the observed data distribution $P \in \mathcal{P}$. In this section, to introduce the concept of super learning, we simply consider estimation of the function Λ_j . The parameter $\Psi : \mathcal{P} \rightarrow \mathcal{M}$ is then identified via equation (3) by $\Psi(P) = \Lambda_j$.

As input to the super learner we need a sample $\mathcal{D}_n = \{O_i\}_{i=1}^n$ of i.i.d. observations from some unknown $P \in \mathcal{P}$ and a finite collection of candidate learners \mathcal{A} . Each learner $a \in \mathcal{A}$ is a map $a : \mathcal{O}^n \rightarrow \mathcal{M}$ which takes a data set as input and returns an estimate $a(\mathcal{D}_n) \in \mathcal{M}$ of Λ_j . In what follows, we use the short-hand notation $P[f] = \int f(o)P(do)$. A super learner evaluates the performance of $a \in \mathcal{A}$ using a loss function $L : \mathcal{M} \times \mathcal{O} \rightarrow \mathbb{R}_+$ by estimating the expected loss $P[L(a(\mathcal{D}_n), \cdot)]$ using cross-validation. Specifically, the expected loss of $a \in \mathcal{A}$ is estimated by splitting the data set \mathcal{D}_n into K disjoint approximately equally sized subsets $\mathcal{D}_n^1, \mathcal{D}_n^2, \dots, \mathcal{D}_n^K$ and then calculating the cross-validated loss

$$\hat{R}_n(a; L) = \frac{1}{K} \sum_{k=1}^K \frac{1}{|\mathcal{D}_n^k|} \sum_{O_i \in \mathcal{D}_n^k} L(a(\mathcal{D}_n^{-k}), O_i), \quad \text{with } \mathcal{D}_n^{-k} = \mathcal{D}_n \setminus \mathcal{D}_n^k.$$

The subset \mathcal{D}_n^{-k} is referred to as the k 'th training sample, while \mathcal{D}_n^k is referred to as the k 'th test or hold-out sample. The discrete super learner is defined as

$$\hat{a}_n = \operatorname{argmin}_{a \in \mathcal{A}} \hat{R}_n(a; L).$$

The final estimator of $\Psi(P) = \Lambda_j$ is then the selected learner applied to the full data set, i.e., $\hat{a}_n(\mathcal{D}_n)$. The oracle learner is defined as the learner that minimizes the average loss according to the data-generating distribution P , i.e.,

$$\tilde{a}_n = \operatorname{argmin}_{a \in \mathcal{A}} \tilde{R}_n(a; L), \quad \text{with} \quad \tilde{R}_n(a; L) = \frac{1}{K} \sum_{k=1}^K P[L(a(\mathcal{D}_n^{-k}), \cdot)].$$

Note that both the discrete super learner and the oracle learner depend on the library of learners and on the number of folds K , and that the oracle learner is a function of the data and the unknown data-generating distribution. These dependencies are suppressed in the notation.

4 Existing methods

Machine learning based on right-censored data commonly use the negative partial log-likelihood as loss function [e.g., [Li et al., 2016](#), [Yao et al., 2017](#), [Lee et al., 2018](#), [Katzman et al., 2018](#), [Gensheimer and Narasimhan, 2019](#), [Lee et al., 2021](#), [Kvamme and Borgan, 2021](#)]. However, this loss function is unsuited for super learning, because many canonical survival learners (e.g., the Kaplan-Meier estimator, random survival forest, and semi-parametric Cox models) provide cumulative hazard functions that are piece-wise constant in the time argument, and hence assign zero probability to event times not observed in the training data. This implies that when data are observed in continuous time, any of these learners will almost surely have infinite loss in any independent hold-out sample according to the negative partial log-likelihood loss.

When a proportional hazards model is assumed, the baseline hazard function can be profiled out of the likelihood to give a new partial log-likelihood loss [[Cox, 1972](#)], which has been suggested as a loss function for super learning [[Golmakani and Polley, 2020](#), [Verweij and van Houwelingen, 1993](#)]. While this allows the library of learners to include Cox' proportional hazard models, the drawback is that the library is now restricted to include only these models.

Another approach for super learning with right-censored data is to use an inverse probability of censoring weighted (IPCW) loss function [[Graf et al., 1999](#), [van der Laan and Dudoit, 2003](#), [Molinario et al., 2004](#), [Keles et al., 2004](#), [Hothorn et al., 2006](#), [Gerds and Schumacher, 2006](#), [Gonzalez Ginestet et al., 2021](#)]. An IPCW loss function is attractive because the associated risk does not depend on the censoring distribution but describes a feature of the population of interested governed by the measure $Q \in \mathcal{Q}$. Similar results can be obtained using censoring unbiased transformations [[Fan and Gijbels, 1996](#), [Steingrimsson et al., 2019](#)] or pseudo-values [[Andersen et al., 2003](#), [Mogenssen and Gerds, 2013](#), [Sachs et al., 2019](#)]. All these methods rely on an estimator of the censoring distribution, and their drawback is that this estimator has to be pre-specified. When the data-generating mechanism is complex and not well-understood, pre-specification of the censoring distribution is a challenge.

As far as we are aware, the only existing attempt at avoiding the need to pre-specify a censoring model is a recent proposal suggested independently by [Han et al. \[2021\]](#) and [Westling et al. \[2021\]](#). The authors do not consider competing risks but suggest to iterate between learning Λ and Γ using IPCW loss functions and select the final learner when the iterative procedure has converged. To the best of our knowledge, no general theoretical guarantees exist for this procedure. It seems unclear whether this iterative procedure will always be able to find a correctly specified model in a given library.

5 The state learner

The problem with most existing super learners for right-censored data is that they depend on a pre-specified estimator of the censoring distribution. The main idea of the state learner is to jointly use learners of Λ_1 , Λ_2 , and Γ , and the relations in equation (2), to learn a feature of the observed data distribution P . The discrete state learner ranks a tuple of learners of $(\Lambda_1, \Lambda_2, \Gamma)$ based on how well they jointly model the observed data. To formally introduce the state learner, we define the multi-state process

$$\eta(t) = \mathbf{1}\{\tilde{T} \leq t, \tilde{D} = 1\} + 2\mathbf{1}\{\tilde{T} \leq t, \tilde{D} = 2\} + 3\mathbf{1}\{\tilde{T} \leq t, \tilde{D} = 0\}, \quad \text{for } t \in [0, \tau].$$

Note that at time t , we observe that each observation is in one of four mutually exclusive states (Figure 1). The conditional distribution of $\eta(t)$ given $X = x$ is determined by the

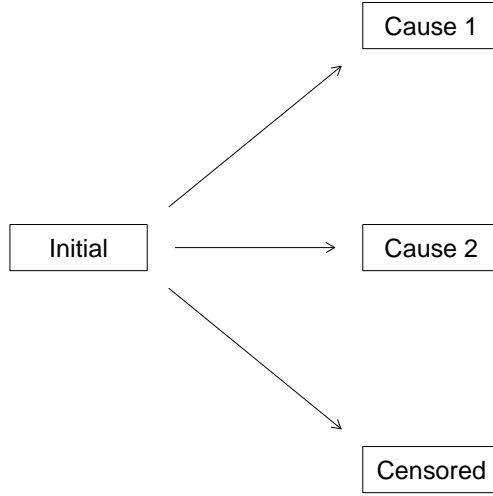


Figure 1: Illustration of the multi-state process η used by the state learner. Note that ‘censored’ is a state, hence the process is always observed at any time.

function

$$F(t, k, x) = P(\eta(t) = k \mid X = x), \quad \text{for all } t \in [0, \tau], k \in \{0, 1, 2, 3\}, x \in \mathcal{X}. \quad (5)$$

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The function F describes the conditional state occupation probabilities corresponding to the observed multi-state process η .

We propose to construct a super learner for F , i.e., the target of this super learner is $\Psi(P) = F$ where the parameter is identified through equation (5). Because each quadruple $(\Lambda_1, \Lambda_2, \Gamma, H)$ characterizes a $P \in \mathcal{P}$ which in turn determines (F, H) , a learner for F can be constructed from learners of Λ_1 , Λ_2 , and Γ as follows:

$$\begin{aligned} F(t, 1, x) &= P(\tilde{T} \leq t, \Delta = 1 \mid X = x) = \int_0^t e^{\{-\Lambda_1(s|x) - \Lambda_2(s|x) - \Gamma(s|x)\}} \Lambda_1(ds \mid x), \\ F(t, 2, x) &= P(\tilde{T} \leq t, \Delta = 2 \mid X = x) = \int_0^t e^{\{-\Lambda_1(s|x) - \Lambda_2(s|x) - \Gamma(s|x)\}} \Lambda_2(ds \mid x), \\ F(t, 3, x) &= P(\tilde{T} \leq t, \Delta = 0 \mid X = x) = \int_0^t e^{\{-\Lambda_1(s|x) - \Lambda_2(s|x) - \Gamma(s|x)\}} \Gamma(ds \mid x), \\ F(t, 0, x) &= P(\tilde{T} > t \mid X = x) = 1 - F(t, 1, x) - F(t, 2, x) - F(t, 3, x). \end{aligned} \quad (6)$$

The state learner requires three libraries of learners, \mathcal{A}_1 , \mathcal{A}_2 , and \mathcal{B} , where \mathcal{A}_1 and \mathcal{A}_2 contain learners of the conditional cause-specific cumulative hazard functions of the event time distribution Λ_1 and Λ_2 , respectively, and \mathcal{B} contains learners of the conditional cumulative hazard function of the censoring distribution. Based on the Cartesian product of libraries of learners for $(\Lambda_1, \Lambda_2, \Gamma)$ we construct a library $\mathcal{F}(\mathcal{A}_1, \mathcal{A}_2, \mathcal{B})$ of learners for F :

$$\mathcal{F}(\mathcal{A}_1, \mathcal{A}_2, \mathcal{B}) = \{\varphi_{a_1, a_2, b} : a_1 \in \mathcal{A}_1, a_2 \in \mathcal{A}_2, b \in \mathcal{B}\},$$

where in correspondance with the relations in equation (6),

$$\begin{aligned}\varphi_{a_1, a_2, b}(\mathcal{D}_n)(t, 1, x) &= \int_0^t e^{\{-a_1(\mathcal{D}_n)(s|x) - a_2(\mathcal{D}_n)(s|x) - b(\mathcal{D}_n)(s|x)\}} a_1(\mathcal{D}_n)(ds | x), \\ \varphi_{a_1, a_2, b}(\mathcal{D}_n)(t, 2, x) &= \int_0^t e^{\{-a_1(\mathcal{D}_n)(s|x) - a_2(\mathcal{D}_n)(s|x) - b(\mathcal{D}_n)(s|x)\}} a_2(\mathcal{D}_n)(ds | x), \\ \varphi_{a_1, a_2, b}(\mathcal{D}_n)(t, 3, x) &= \int_0^t e^{\{-a_1(\mathcal{D}_n)(s|x) - a_2(\mathcal{D}_n)(s|x) - b(\mathcal{D}_n)(s|x)\}} b(\mathcal{D}_n)(ds | x), \\ \varphi_{a_1, a_2, b}(\mathcal{D}_n)(t, 0, x) &= 1 - \sum_{j=1}^3 \varphi_{a_1, a_2, b}(\mathcal{D}_n)(t, j, x).\end{aligned}$$

To evaluate how well a function F predicts the observed multi-state process we use the integrated Brier score $\bar{B}_\tau(F, O) = \int_0^\tau B_t(F, O) dt$, where B_t is the Brier score [Brier et al., 1950] at time $t \in [0, \tau]$,

$$B_t(F, O) = \sum_{j=0}^3 (F(t, j, X) - \mathbb{1}\{\eta(t) = j\})^2.$$

As described in Section 3, each learner $\varphi_{a_1, a_2, b}$ in the library $\mathcal{F}(\mathcal{A}_1, \mathcal{A}_2, \mathcal{B})$ is evaluated using the cross-validated loss,

$$\hat{R}_n(\varphi_{a_1, a_2, b}; \bar{B}_\tau) = \frac{1}{K} \sum_{k=1}^K \frac{1}{|\mathcal{D}_n^k|} \sum_{O_i \in \mathcal{D}_n^k} \bar{B}_\tau(\varphi_{a_1, a_2, b}(\mathcal{D}_n^{-k}), O_i),$$

and the discrete state learner is

$$\hat{\varphi}_n = \underset{(a_1, a_2, b) \in \mathcal{A}_1 \times \mathcal{A}_2 \times \mathcal{B}}{\operatorname{argmin}} \hat{R}_n(\varphi_{a_1, a_2, b}; \bar{B}_\tau).$$

6 Theoretical results for the state learner

In this section we establish theoretical guarantees for the state learner. Proposition 6.1 can be derived from the fact that the integrated Brier score (also called the continuous ranked probability score) is a strictly proper scoring rule [Gneiting and Raftery, 2007]. This implies that if we minimize the average loss of the integrated Brier score, we recover the parameters of the data-generating distribution. In particular, the oracle of a state learner will be consistent if the library of learners contains at least one learner that is consistent for estimation of F . Recall that the function F implicitly depends on the data generating probability measure $P \in \mathcal{P}$ but that this was suppressed in the notation. We now make this dependence explicit by writing F_0 for the function which is obtained by substituting a specific $P_0 \in \mathcal{P}$ for P in equation (6).

Proposition 6.1. For $P_0 \in \mathcal{P}$ define

$$F^* = \operatorname{argmin}_F P_0[\bar{B}_\tau(F, \cdot)],$$

where the minimum is taken over all F , such that F is a conditional state occupation probability function for some measure P as defined in equation (5). Then $F^*(t, j, \cdot) = F_0(t, j, \cdot)$ H -almost surely for any $j \in \{0, 1, 2, 3\}$ and almost any $t \in [0, \tau]$.

Proof. See Appendix A. □

We establish a finite sample oracle result for the state learner. Our Corollary 6.2 is in essence a special case of a general cross-validation result by van der Vaart et al. [2006]. We assume that we split the data into equally sized folds, and for simplicity of presentation we take n to be such that $|\mathcal{D}_n^{-k}| = n/K$ with K fixed. We will allow the number of learners to grow with n and write $\mathcal{F}_n = \mathcal{F}(\mathcal{A}_{1,n}, \mathcal{A}_{2,n}, \mathcal{B}_n)$ as short-hand notation and to emphasize the dependence on n . In the following we let $\|\cdot\|_{P_0}$ denote the norm

$$\|F\|_{P_0} = \left\{ \sum_{j=0}^3 \int_{\mathcal{X}} \int_0^\tau F(t, j, x)^2 dt H_0(dx) \right\}^{1/2}. \quad (7)$$

Corollary 6.2. For all $P_0 \in \mathcal{P}$, $n \in \mathbb{N}$, $k \in \{1, \dots, K\}$, and $\delta > 0$,

$$\begin{aligned} \mathbb{E}_{P_0} [\|\hat{\varphi}_n(\mathcal{D}_n^{-k}) - F_0\|_{P_0}^2] &\leq (1 + 2\delta) \mathbb{E}_{P_0} [\|\tilde{\varphi}_n(\mathcal{D}_n^{-k}) - F_0\|_{P_0}^2] \\ &\quad + (1 + \delta) 16K\tau \left(13 + \frac{12}{\delta} \right) \frac{\log(1 + |\mathcal{F}_n|)}{n}. \end{aligned}$$

Proof. See Appendix A. □

Corollary 6.2 has the following asymptotic consequences.

Corollary 6.3. Assume that $|\mathcal{F}_n| = O(n^q)$, for some $q \in \mathbb{N}$ and that there exists a sequence $\varphi_n \in \mathcal{F}_n$, $n \in \mathbb{N}$, such that $\mathbb{E}_{P_0} [\|\varphi_n(\mathcal{D}_n^{-k}) - F_0\|_{P_0}^2] = O(n^{-\alpha})$, for some $\alpha \leq 1$.

(i) If $\alpha = 1$ then $\mathbb{E}_{P_0} [\|\hat{\varphi}_n(\mathcal{D}_n^{-k}) - F_0\|_{P_0}^2] = O(\log(n)n^{-1})$.

(ii) If $\alpha < 1$ then $\mathbb{E}_{P_0} [\|\hat{\varphi}_n(\mathcal{D}_n^{-k}) - F_0\|_{P_0}^2] = O(n^{-\alpha})$.

Proof. See Appendix A. □

In Section 7 we demonstrate how the state learner can be used for targeted learning. A targeted estimator is typically obtained from estimators of the nuisance parameters Λ_1 , Λ_2 , and Γ . By equations (3) and (4) and the definition of F , we have

$$\Gamma(t, x) = \int_0^t \frac{F(ds, 3, x)}{F(s-, 0, x)}, \quad \text{and} \quad \Lambda_j(t, x) = \int_0^t \frac{F(ds, j, x)}{F(s-, 0, x)}, \quad j \in \{1, 2\}, \quad (8)$$

and thus a targeted estimator can also be obtained from an estimator of F using equation (8). The key feature of a targeted estimator is that it is asymptotically equivalent to a sum of i.i.d. random variables plus a second order remainder term [Bickel et al., 1993, Fisher

and Kennedy, 2021]. For our setting of competing risks, the remainder term is typically dominated by terms of the form

$$P \left[\int_0^\tau w_n(s, \cdot) \hat{M}_{1,n}(s \mid \cdot) \hat{M}_{2,n}(ds \mid \cdot) \right], \quad (9)$$

where $(\hat{M}_{1,n}, \hat{M}_{2,n})$ is any of the nine combinations of $\hat{M}_{1,n} \in \{\Gamma - \hat{\Gamma}_n, [\Lambda_1 - \hat{\Lambda}_{1,n}], [\Lambda_2 - \hat{\Lambda}_{2,n}]\}$ and $\hat{M}_{2,n} \in \{\Gamma - \hat{\Gamma}_n, [\Lambda_1 - \hat{\Lambda}_{1,n}], [\Lambda_2 - \hat{\Lambda}_{2,n}]\}$, and w_n is some data-dependent function with domain $[0, \tau] \times \mathcal{X}$ [van der Laan and Robins, 2003]. In particular, a targeted estimator will be asymptotically linear if the ‘products’ of the estimation errors $\hat{M}_{1,n}$ and $\hat{M}_{2,n}$ in equation (9) are $o_P(n^{-1/2})$. Proposition 6.4 states that if equation (9) holds for the a targeted estimator based on estimators $\hat{\Lambda}_{1,n}$, $\hat{\Lambda}_{2,n}$, and $\hat{\Gamma}_n$, then a similar product structure holds for a targeted estimator based on \hat{F}_n . We state the result for the special case that $\hat{M}_{1,n} = \Gamma - \hat{\Gamma}_n$ and $\hat{M}_{2,n} = \Lambda_1 - \hat{\Lambda}_{1,n}$, but similar results holds for any combinations of $\Gamma - \hat{\Gamma}_n$, $\Lambda_1 - \hat{\Lambda}_{1,n}$, and $\Lambda_2 - \hat{\Lambda}_{2,n}$.

Proposition 6.4. *Assume that $w(s, x) \leq c$, $F(s, 0, x) \geq 1/c$ and $\hat{F}_n(s, 0, x) \geq 1/c$ for some $c > 0$ for all $s \in [0, \tau]$ and $x \in \mathcal{X}$. Then there are real-valued uniformly bounded functions w_n^a , w_n^b , w_n^c , and w_n^d with domain $[0, \tau]^2 \times \mathcal{X}$ such that*

$$\begin{aligned} & P_0 \left[\int_0^\tau w(s, \cdot) \left\{ \Gamma_0(s, \cdot) - \hat{\Gamma}_n(s, \cdot) \right\} [\Lambda_0 - \hat{\Lambda}_n](ds, \cdot) \right] \\ &= P_0 \left[\int_0^\tau \int_0^s w_n^a(s, u, \cdot) [F_0 - \hat{F}_n](u-, 0, \cdot) [F_0 - \hat{F}_n](s-, 0, \cdot) F_0(du, 2, \cdot) F_0(ds, 1, \cdot) \right] \\ &+ P_0 \left[\int_0^\tau \int_0^s w_n^b(s, u, \cdot) [F_0 - \hat{F}_n](u-, 0, \cdot) F_0(du, 2, \cdot) [F_0 - \hat{F}_n](ds, 1, \cdot) \right] \\ &+ P_0 \left[\int_0^\tau \int_0^s w_n^c(s, u, \cdot) [F_0 - \hat{F}_n](du, 2, \cdot) [F_0 - \hat{F}_n](s-, 0, \cdot) F_0(ds, 1, \cdot) \right] \\ &+ P_0 \left[\int_0^\tau \int_0^s w_n^d(s, u, \cdot) [F_0 - \hat{F}_n](du, 2, \cdot) [F_0 - \hat{F}_n](ds, 1, \cdot) \right]. \end{aligned}$$

Proof. See Appendix B. □

7 Targeted learning

Features of the observed data distribution $P \in \mathcal{P}$ are rarely of interest. We are instead interested in a parameter $\theta: \mathcal{Q} \rightarrow \Theta$ that expresses a property of the uncensored population governed by the measure $Q \in \mathcal{Q}$. The parameter space Θ can be a subset of \mathbb{R}^d or a subset of a function space, such as \mathcal{M} . In subsection 7.1 we give a concrete example from causal inference where θ is the average treatment effect and $\Theta = [-1, 1]$. Under the assumption of conditional independent censoring and positivity, θ is identifiable from \mathcal{P} which means that there exists an operator $\Psi: \mathcal{P} \rightarrow \Theta$ such that $\theta(Q) = \Psi(P_{Q,\Gamma})$ for all $\Gamma \in \mathcal{M}$. By equation (2) this imply that we may write

$$\theta(Q) = \Psi(P) = \tilde{\Psi}^0(\Lambda_1, \Lambda_2, H),$$

for some operator $\tilde{\Psi}^0$. The state learner provides a ranking of tuples $(a_1, a_2, b) \in \mathcal{A}_1 \times \mathcal{A}_2 \times \mathcal{B}$, and we use $\hat{a}_{1,n}$, $\hat{a}_{2,n}$, and \hat{b}_n to denote the learners corresponding to the discrete state learner $\hat{\varphi}_n$. Letting $H(\mathcal{D}_n)$ denote the empirical measure of $\{X_1, \dots, X_n\}$, we can obtain a simple plug-in an estimator of θ as

$$\hat{\Psi}^0(\mathcal{D}_n) = \tilde{\Psi}^0(\hat{a}_{1,n}(\mathcal{D}_n), \hat{a}_{2,n}(\mathcal{D}_n), H(\mathcal{D}_n)). \quad (10)$$

The asymptotic distribution of $\hat{\Psi}_{\tau,j}^0$ is difficult to analyze due to the model selection step involved when estimating the nuisance parameters Λ_1 and Λ_2 . In addition, the estimator will typically have an asymptotic bias that vanishes at a sub-optimal rate. Using tools from semi-parametric efficiency theory, it is possible to construct a so-called targeted or debiased estimator with smaller asymptotic bias and an asymptotic distribution which we know how to estimate [Bickel et al., 1993, van der Laan and Rose, 2011, Chernozhukov et al., 2018]. A targeted estimator is based on the efficient influence function for the parameter $\tilde{\Psi}^0$ and relies on an estimator of Γ in addition to estimators of Λ_1 and Λ_2 . The efficient influence function is a P -zero mean and square integrable function indexed by the nuisance parameters $(\Lambda_1, \Lambda_2, \Gamma)$, which we denote by $\psi(\cdot; \Lambda_1, \Lambda_2, \Gamma)$. The name is justified because any regular asymptotically linear estimator that has ψ as its influence function is efficient, meaning that it has smallest asymptotic variance among all regular asymptotically linear estimators.

An example of a targeted estimator is the one-step estimator, defined as

$$\hat{\Psi}_{\text{OS}}(\mathcal{D}_n) = \tilde{\Psi}^0(\hat{a}_{1,n}(\mathcal{D}_n), \hat{a}_{2,n}(\mathcal{D}_n), H(\mathcal{D}_n)) + \mathbb{P}_n[\psi(\cdot; \hat{a}_{1,n}(\mathcal{D}_n), \hat{a}_{2,n}(\mathcal{D}_n), \hat{b}_n(\mathcal{D}_n))], \quad (11)$$

where \mathbb{P}_n is the empirical measure of a sample $\{O_i\}_{i=1}^n$. We can make the following asymptotic expansion of the one-step estimator [Pfanzagl and Wefelmeyer, 1982, van der Laan and Robins, 2003, Fisher and Kennedy, 2021, Kennedy, 2022, Rytgaard et al., 2022],

$$\hat{\Psi}_{\text{OS}}(\mathcal{D}_n) - \Psi(P) = \mathbb{P}_n[\psi(\cdot; \Lambda_1, \Lambda_2, \Gamma)] + \text{Rem}(\hat{\Lambda}_{1,n}, \hat{\Lambda}_{2,n}, \hat{\Gamma}_n, P) + o_P(n^{-1/2}),$$

where the remainder term is typically such that

$$\text{Rem}(\hat{\Lambda}_{1,n}, \hat{\Lambda}_{2,n}, \hat{\Gamma}_n, P) = \mathcal{O}_P\left\{\|\Lambda_1 - \hat{\Lambda}_{1,n}\|^2 + \|\Lambda_2 - \hat{\Lambda}_{2,n}\|^2 + \|\Gamma - \hat{\Gamma}_n\|^2\right\}, \quad (12)$$

for some suitable norm $\|\cdot\|$, for instance the \mathcal{L}_P^2 -norm. Hence, under a suitable Donsker class regularity condition [Bickel et al., 1993, Kennedy, 2016], when equation (12) holds and the nuisance parameters Λ_1 , Λ_2 , and Γ are consistently estimated at rate $o_P(n^{-1/4})$, then

$$\sqrt{n}(\hat{\Psi}_{\text{OS}}(\mathcal{D}_n) - \Psi(P)) \rightsquigarrow \mathcal{N}(0, P[\psi(\cdot; \Lambda_1, \Lambda_2, \Gamma)^2]), \quad (13)$$

where we use \rightsquigarrow to denote weak convergence [van der Vaart, 2000]. In particular, equation (13) and Slutsky's lemma imply that we can obtain asymptotically valid $(1 - \alpha) \cdot 100\%$ confidence intervals by calculating

$$\left[\hat{\Psi}_{\text{OS}}(\mathcal{D}_n) - q_{\alpha/2} \hat{\sigma}(\mathcal{D}_n), \hat{\Psi}_{\text{OS}}(\mathcal{D}_n) + q_{\alpha/2} \hat{\sigma}(\mathcal{D}_n) \right],$$

where q_α is the $(1 - \alpha)$ -quantile of the standard normal distribution, and

$$\hat{\sigma}(\mathcal{D}_n) = \left(\mathbb{P}_n \left[\psi(\cdot; \hat{a}_{1,n}(\mathcal{D}_n), \hat{a}_{2,n}(\mathcal{D}_n), \hat{b}_n(\mathcal{D}_n))^2 \right] \right)^{1/2}.$$

7.1 Average treatment effect on the cumulative incidence

In the following we demonstrate how the state learner and the general estimation strategy outlined above can be used to construct an estimator of the cause-specific average treatment effect. We assume that the covariate vector $X \in \mathbb{R}^p$ can be separated into a binary treatment indicator A and a vector of potential confounders, $W \in \mathcal{W} \subset \mathbb{R}^{p-1}$. We abuse notation slightly by writing $\Lambda_j(t | x) = \Lambda_j(t | a, w)$ and $S(t | x) = S(t | a, w)$ when $x = (a, w)$. We use μ to denote the marginal distribution of W and π to denote the conditional probability of treatment,

$$\pi(w) = P(A = 1 | W = w).$$

We assume throughout that π is uniformly bounded away from 0 and 1 on \mathcal{W} . As both A and W are fully observed for all individuals we can use an existing super learner to estimate π [Polley et al., 2023], and we denote this estimator by $\hat{\pi}_n$. We use the empirical measure of $\{W_1, \dots, W_n\}$ to estimate μ , and denote this estimator by the $\hat{\mu}_n$. As parameter of interest we consider the standardized difference in the cumulative incidence due to cause 1 at time τ , which can be expressed as

$$\theta_\tau(Q) = \int_{\mathcal{W}} \left\{ \int_0^\tau S(s- | w, 1) \Lambda_1(ds | w, 1) - \int_0^\tau S(s- | w, 0) \Lambda_1(ds | w, 0) \right\} \mu(dw).$$

Under a set of additional assumptions, θ_τ can be given the causal interpretation

$$\theta_\tau(Q) = P(T^{A=1} \leq \tau, D^{A=1} = 1) - P(T^{A=0} \leq \tau, D^{A=0} = 1),$$

where (T^A, D^A) denotes potential outcomes [Hernán and Robins, 2020]. In this case, the interpretation of θ_τ is the difference in the average risk of cause 1 occurring before time τ in the population if everyone had been given treatment ($A = 1$) compared to if no one had been given treatment.

Using equation (1), we may write $\theta_\tau(Q) = \tilde{\Psi}_t^0(\Lambda_1, \Lambda_2, \mu)$, where

$$\begin{aligned} \tilde{\Psi}_t^0(\Lambda_1, \Lambda_2, \mu) &= \int_{\mathcal{W}} \int_0^\tau e^{-\Lambda_1(s-|w,1) - \Lambda_2(s-|w,1)} \Lambda_1(ds | w, 1) \mu(dw) \\ &\quad - \int_{\mathcal{W}} \int_0^\tau e^{-\Lambda_1(s-|w,0) - \Lambda_2(s-|w,0)} \Lambda_1(ds | w, 0) \mu(dw). \end{aligned} \quad (14)$$

The efficient influence function for the parameter $\tilde{\Psi}_\tau$ depends on the set $(\Lambda_1, \Lambda_2, \Gamma, \pi)$ of nuisance parameters. Define the quantities

$$\begin{aligned} \omega_a(A, W; \pi) &= \frac{\mathbb{1}\{A = a\}}{\pi(W)^a (1 - \pi(W))^{1-a}}, \\ g(t, A, W; \Lambda_1, \Lambda_2) &= \int_0^t e^{-\Lambda_1(s-|W,A) - \Lambda_2(s-|W,A)} \Lambda_1(ds | W, A), \\ M_j(dt | A, W; \Lambda_j) &= N_j(dt) - \mathbb{1}\{\tilde{T} \geq t\} \Lambda_j(dt | W, A), \quad j \in \{1, 2\}, \end{aligned}$$

and

$$M(dt | A, W; \Lambda_1, \Lambda_2) = M_1(dt | A, W; \Lambda_1) + M_2(dt | A, W; \Lambda_2).$$

The efficient influence function can then be written as [van der Laan and Robins, 2003, Jewell et al., 2007, Rytgaard and van der Laan, 2022],

$$\psi_\tau(O; \Lambda_1, \Lambda_2, \Gamma, \pi) = \psi_\tau^1(O; \Lambda_1, \Lambda_2, \Gamma, \pi) - \psi_\tau^0(O; \Lambda_1, \Lambda_2, \Gamma, \pi) - \tilde{\Psi}_t^0(\Lambda_1, \Lambda_2, \mu),$$

where

$$\begin{aligned} &\psi_\tau^a(O; \Lambda_1, \Lambda_2, \Gamma, \pi) \\ &= \omega_a(A, W; \pi) \int_0^\tau e^{\Gamma(t-|A,W)} M_1(dt | A, W; \Lambda_1) \\ &\quad - \omega_a(A, W; \pi) g(\tau, A, W; \Lambda_1, \Lambda_2) \int_0^\tau e^{[\Gamma + \Lambda_1 + \Lambda_2](t-|A,W)} M(dt | A, W; \Lambda_1, \Lambda_2) \\ &\quad + \omega_a(A, W; \pi) \int_0^\tau g(t, A, W; \Lambda_1, \Lambda_2) e^{[\Gamma + \Lambda_1 + \Lambda_2](t-|A,W)} M(dt | A, W; \Lambda_1, \Lambda_2) \\ &\quad + g(\tau, a, W; \Lambda_1, \Lambda_2). \end{aligned} \quad (15)$$

Equations (14) and (15) allow us to construct a one-step estimator by using the definition given in equation (11), which gives the estimator

$$\begin{aligned}\hat{\Psi}_{t,\text{OS}}(\mathcal{D}_n) &= \tilde{\Psi}_t^0(\hat{a}_1(\mathcal{D}_n), \hat{a}_2(\mathcal{D}_n), \hat{\mu}_n(\mathcal{D}_n)) \\ &\quad + \mathbb{P}_n[\psi_\tau(\cdot; \hat{a}_{1,n}(\mathcal{D}_n), \hat{a}_{2,n}(\mathcal{D}_n), \hat{b}_n(\mathcal{D}_n), \hat{\pi}_n(\mathcal{D}_n))] \\ &= \mathbb{P}_n[\psi_\tau^1(\cdot; \hat{a}_{1,n}(\mathcal{D}_n), \hat{a}_{2,n}(\mathcal{D}_n), \hat{b}_n(\mathcal{D}_n), \hat{\pi}_n(\mathcal{D}_n))] \\ &\quad - \mathbb{P}_n[\psi_\tau^0(\cdot; \hat{a}_{1,n}(\mathcal{D}_n), \hat{a}_{2,n}(\mathcal{D}_n), \hat{b}_n(\mathcal{D}_n), \hat{\pi}_n(\mathcal{D}_n))].\end{aligned}\tag{16}$$

8 Numerical experiments

As a proof of concept we conduct two small simulation studies in a setting without competing risks. We generate data according to a distribution motivated from a real dataset in which censoring depends on the baseline covariates. We simulate data based on a prostate cancer study described in [Kattan et al., 2000]. The outcome of interest was the time to tumor recurrence, and five baseline covariates were used to predict outcome: prostate-specific antigen (PSA, ng/mL), Gleason score sum (GSS, values between 6 and 10), radiation dose (RD), hormone therapy (HT, yes/no) and clinical stage (CS, six values). The study was designed such that a patient’s radiation dose depended on when the patient entered the study [Gerds et al., 2013]. This in turn implied that the time of censoring depended on the radiation dose. The data were re-analyzed in [Gerds et al., 2013] where a sensitivity analysis was conducted based on simulated data. We use the same simulation setup, where event and censoring times are generated according to parametric Cox-Weibull models estimated from the original data, and the covariates are generated according to either marginal Gaussian normal or binomial distributions estimated from the original data [c.f., Gerds et al., 2013, Section 4.6]. We refer to this simulation setting as “dependent censoring”. We also considered a simulation setting where data were generated in the same way, except that censoring was generated completely independently. We refer to this simulation setting as “independent censoring”.

For all super learners we use a library consisting of three learners: The Kaplan-Meier estimator [Kaplan and Meier, 1958, Gerds, 2019], a Cox model with main effects [Cox, 1972, Therneau, 2022], and a random survival forest [Ishwaran et al., 2008, Ishwaran and Kogalur, 2023]. We use the same library to learn the outcome and the censoring mechanism. To be precise, note that given a learner for the cumulative hazard function of the outcome event, we can typically use the same method to construct a learner of the cumulative hazard function of the censoring distribution. This would typically work by training the learner on the data set \mathcal{D}_n^c , where $\mathcal{D}_n^c = \{O_i^c\}_{i=1}^n$ with $O_i^c = (\tilde{T}_i, 1 - \Delta, X_i)$. When we say that we use a learner for the cumulative hazard function of the outcome to learn the cumulative hazard function of the censoring time, we mean that the learner is trained on \mathcal{D}_n^c .

We first compare the state learner to two IPCW based super learners: The first uses a Cox model with main effects to estimate the censoring probabilities (IPCW(Cox)), while the second uses the Kaplan-Meier estimator to estimate the censoring probabilities (IPCW(KM)). The Cox model for the censoring distribution is correctly specified in both simulation settings while the Kaplan Meier estimator only estimates the censoring model correctly in the simulation setting where censoring is independent. Both IPCW super learners are fitted using the R-package `riskRegression` [Gerds et al., 2023]. Each super learner provides a learner for the cumulative hazard function for the outcome of interest, and from this a risk prediction model can be obtained. We measure performance of each super learner by calculating the index of prediction accuracy (IPA) [Kattan and Gerds, 2018] at a fixed time horizon (36 months) for the risk prediction model provided by the super learner. The IPA

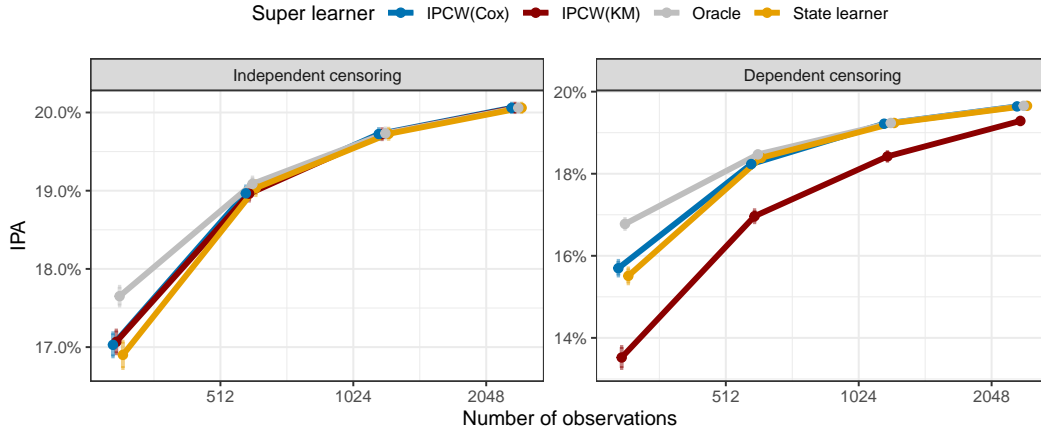


Figure 2: For the risk prediction models provided by each of the super learners, the IPA is plotted against sample size. The results are based on 1000 repetitions and the error bars are used to quantify the Monte Carlo uncertainty.

is 1 minus the ratio between the model’s Brier score and the null model’s Brier score, where the null model is the model that does not use any covariate information. The IPA is approximated using a large ($n = 20,000$) independent data set of uncensored data. As a benchmark we calculate the performance of the risk prediction model chosen by the oracle selector. The oracle selector uses the large data set of uncensored event times to select the learner with the highest IPA.

The results are shown in Figure 2. We see that when censoring is not independent, using the Kaplan-Meier estimator to estimate the censoring probabilities provides a risk prediction model with an IPA that is lower than the risk prediction model provided by the state learner. The performance of the risk prediction model selected by the state learner is similar to the risk prediction model selected by the IPCW(Cox) super learner which a priori uses a correctly specified model for the censoring distribution. Both these risk prediction models are close to the performance of the oracle, except for small sample sizes.

We next compare the state learner to the super learner `survSL` [Westling et al., 2021], as this is the only existing super learner we know which works without a pre-specified censoring model. As both the state learner and `survSL` also provides a prediction model for the probability of being censored, we compare the performance of both the outcome and the censoring modeling using the IPA.

The results are shown in Figure 3. We see that the prediction models selected for both censoring and outcome have similar or higher API compared to the prediction models selected by `survSL` for most sample sizes.

9 Example with prostate cancer study

The prostate cancer data analyzed by Kattan et al. [2000], which we introduced in Section 8, include a competing event in the form of death without tumor recurrence. For illustration, we fit the state learner to the original data set consisting of 1,042 patients. We consider death without tumor recurrence and recurrence of tumor as two competing events of interest. We include the five learner KM, Cox, strata, CS, Lasso, Elastic, and RF which are described

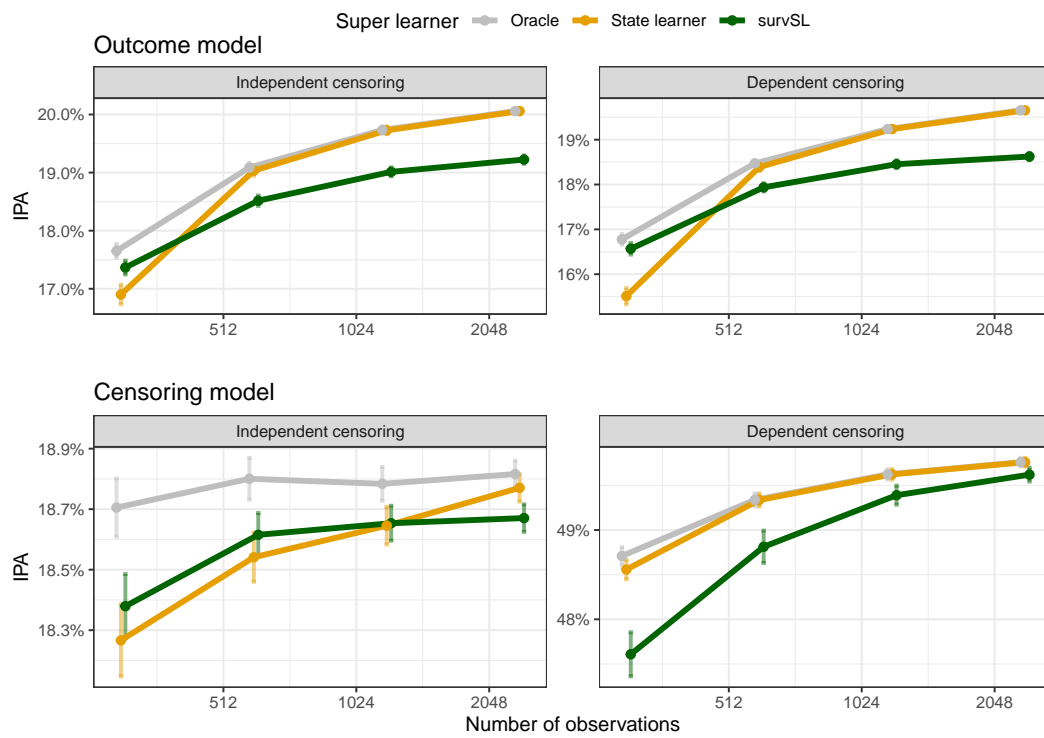


Figure 3: For the risk prediction models of both the outcome and the censoring probability provided by each of the super learners, the IPA is plotted against sample size. The results are based on 1000 repetitions and the error bars are used to quantify the Monte Carlo uncertainty.

in Table 1. We use the same library of learners to learn Λ_1 , Λ_2 , and Γ . In this case, Λ_1 denotes the cause-specific cumulative hazard function of tumor recurrence, and Λ_2 denotes the cause-specific cumulative hazard function of death without tumor recurrence.

Family	Model	Description
Marginal	KM	The Kaplan-Meier estimator
Cox	Cox	All five covariates included with additive effects
	Cox strata CS	Cox model stratified on CS
Penalized Cox	Lasso	Cox model with L_1 -norm penalty
	Elastic	Cox model with L_1 - and L_2 -norm penalty
Random forest	RF	Random forest with default settings

Table 1: Overview of the five learners used by the state learner when applied to the prostate cancer data set. The Kaplan-Meier estimator was fitted using the package `prodlim` [Gerds, 2019]. All Cox models included all five covariates in the model and were fitted using the package `survival` [Therneau, 2022]. All penalized Cox models included all five covariates as linear predictors and were fitted using the package `glmnet` [Simon et al., 2011, Friedman et al., 2010]. The random forest was fitted with the package `randomForestSRC` [Ishwaran and Kogalur, 2023].

This gives a library consisting of $5^3 = 125$ learners for the conditional state occupation probability function F defined in equation (5). We use five folds for training and testing the models, and we repeat training and evaluation five times with different splits. The integrated Brier score (defined in Section 5) for all learners are shown in Figure 4, and the top 10 combinations of learners are displayed in Table 2. We see that the prediction performance is mostly affected by the choice of learner for the censoring distribution. Several combinations of learners give similar performance as measured by the integrated Brier score, as long as a random forest is used to model the censoring distribution.

Tumor learner	Death learner	Censoring learner	Integrated Brier score
RF	KM	RF	7.02 ± 0.05
Cox strata CT	Elastic	RF	7.03 ± 0.03
RF	Elastic	RF	7.03 ± 0.05
RF	RF	RF	7.03 ± 0.05
Cox strata CT	Lasso	RF	7.03 ± 0.03
RF	Lasso	RF	7.03 ± 0.05
Elastic	Elastic	RF	7.03 ± 0.03
Lasso	Elastic	RF	7.03 ± 0.03
Elastic	Lasso	RF	7.03 ± 0.03
Lasso	Lasso	RF	7.03 ± 0.03

Table 2: The 10 best performing models in terms of integrated Brier score. The reported standard errors are based on five repetitions using different splits. The models are described in Table 1. We refer to learners of Λ_1 , Λ_2 , and Γ as ‘Tumor learner’, ‘Death learner’, and ‘Censoring learner’, respectively.

As an illustration, we use the learners of the three cumulative hazard functions selected by the state learner and the estimator defined in Section 7.1, equation (16), to estimate the average treatment effect of hormone therapy on risk of tumor recurrence and death. The results are shown in Figure 5 for 6 month intervals after baseline with point wise 95% confidence intervals. We see that hormone therapy appears to decrease the risk of tumor recurrence and increase the risk of death without tumor recurrence, but that not of the estimated effects are significant.

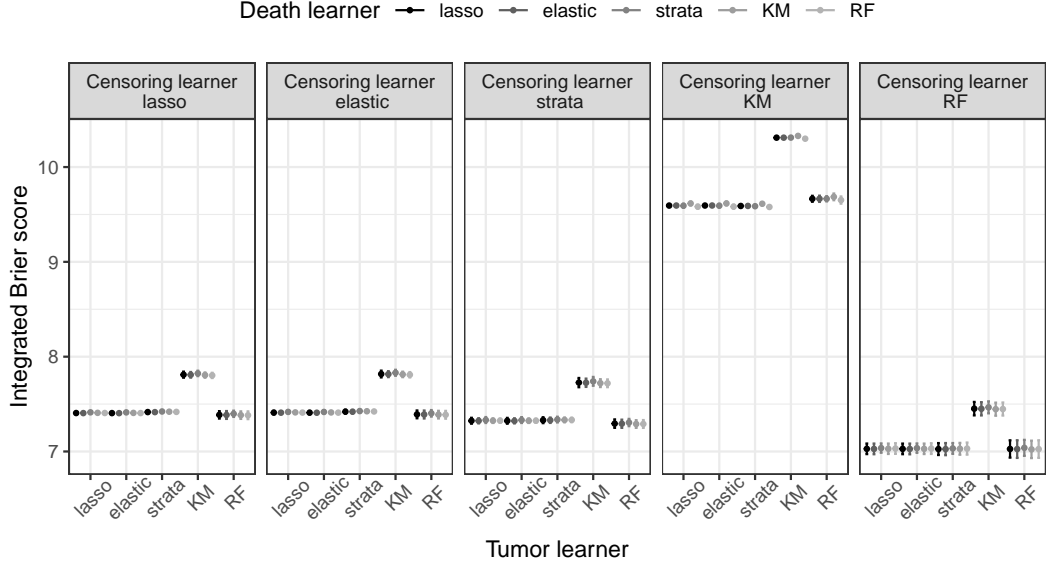


Figure 4: The results of applying the 125 combinations of learners to the prostate cancer data set. The learners are KM (KM), Cox strata CS (strata), Lasso (lasso), Elastic (elastic), and RF (RF) as described Table 1. The error bars are based on five repetitions using different splits. We refer to learners of Λ_1 , Λ_2 , and Γ as ‘Tumor learner’, ‘Death learner’, and ‘Censoring learner’, respectively.

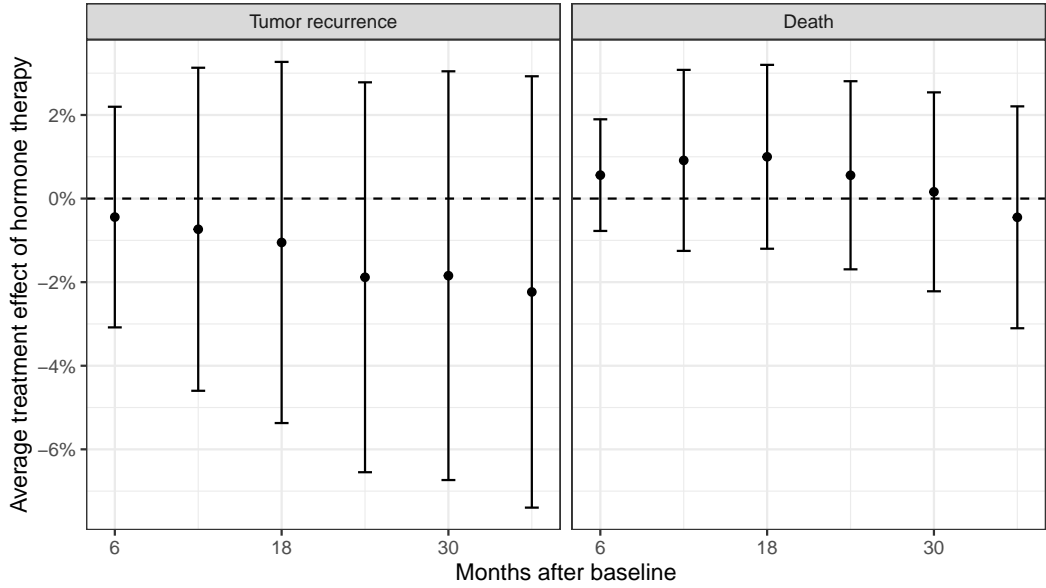


Figure 5: Estimates of the average treatment effect of hormone therapy on the risk of tumor recurrence and death obtained from the prostate cancer study analyzed by Kattan et al. [2000]. The estimates are based on the estimator defined in equation (16) with point wise 95% confidence intervals calculated as described in Section 7. The estimates of the nuisance parameters are provided by the state learner.

10 Discussion

We have proposed a new super learner that can be used with right-censored data and competing events. Compared to existing methods, the advantage of the state learner is that it does not depend on a pre-specified estimator of the censoring distribution, but selects one automatically based on the provided library \mathcal{B} . Furthermore, the state learner neither requires evaluation of the density of Λ_j nor assumes a particular semi-parametric structure for Λ_j . In the remainder of this section we point to some limitations of our proposal and discuss avenues for further research.

A major advantage of the state learner is that performance of each combination of learners is measured in terms of observable quantities. This means that no additional nuisance parameters need to be estimated to evaluate the loss. The drawback with this approach is that we are rarely interested in features of the observed data distribution when the data are right-censored. The finite sample oracle inequality in Corollary 6.2 concerns the function F , which is a feature of $P \in \mathcal{P}$, while what we are typically interested in is Λ_j or S , which are features of $Q \in \mathcal{Q}$. We emphasize that while the state learner provides us with estimates of Λ_j and Γ based on libraries \mathcal{A}_j and \mathcal{B} , performance are not assessed directly for these parameters, but only jointly for estimation of the parameter F . For settings without a competing risk, our numerical studies suggest that measuring performance with respect to estimation of F also leads to good performance for estimation of S . Further research on this topic, both numerical and theoretical, is warranted.

Our proposed super learner can be implemented with a broad library of learners using existing software, for instance the R-package `riskRegression` [Gerds et al., 2023]. Furthermore, while the library $\mathcal{F}(\mathcal{A}_1, \mathcal{A}_2, \mathcal{B})$ consists of $|\mathcal{A}_1||\mathcal{A}_2||\mathcal{B}|$ learners, as long as we have sufficient memory we need only fit $|\mathcal{A}_1| + |\mathcal{A}_2| + |\mathcal{B}|$ learners in each fold. To evaluate the performance of each learner we need to perform $|\mathcal{A}_1||\mathcal{A}_2||\mathcal{B}|$ operations to calculate the integrated Brier score in each hold-out sample, one for each combination of the fitted models, but these operations are often negligible compared to fitting the models. Hence the state learner is essentially no more computationally demanding than any procedure that uses super learning to learn Λ_1 , Λ_2 , and Γ separately. While our proposal is based on constructing the library \mathcal{F} from libraries for learning Λ_1 , Λ_2 , and Γ , it would also be of interest to consider learners that estimate F directly.

In our numerical studies, we only considered learners of Λ_j and Γ that provide cumulative hazard functions which are piece-wise constant in the time argument. This simplifies the calculation of F as the integrals in equation (6) reduce to sums. When Λ_j or Γ are absolutely continuous in the time argument, calculating F is more involved, but we expect that a good approximation can be achieved by discretization. In the future, we intend to investigate the performance of the state learner when using a broader library of learners in more comprehensive simulation studies.

A Theoretical guarantees for the state learner

In this section we provide proofs of the results stated in Section 6.

Define $\bar{B}_{\tau,0}(F, o) = \bar{B}_{\tau}(F, o) - \bar{B}_{\tau}(F_0, o)$ and $R_0(F) = P_0[\bar{B}_{\tau,0}(F, \cdot)]$.

Lemma A.1. $R_0(F) = \|F - F_0\|_{P_0}^2$, where $\|\cdot\|_{P_0}$ is defined in equation (7).

Proof. For any $t \in [0, \tau]$ and $k \in \{0, 1, 2\}$ we have

$$\begin{aligned}
& \mathbb{E}_{P_0} [(F(t, k, X) - \mathbf{1}\{\eta(t) = k\})^2] \\
&= \mathbb{E}_{P_0} [(F(t, k, X) - F_0(t, k, X) + F_0(t, k, X) - \mathbf{1}\{\eta(t) = k\})^2] \\
&= \mathbb{E}_{P_0} [(F(t, k, X) - F_0(t, k, X))^2] + \mathbb{E}_{P_0} [(F_0(t, k, X) - \mathbf{1}\{\eta(t) = k\})^2] \\
&\quad + 2 \mathbb{E}_{P_0} [(F(t, k, X) - F_0(t, k, X))(F_0(t, k, X) - \mathbf{1}\{\eta(t) = k\})] \\
&= \mathbb{E}_{P_0} [(F(t, k, X) - F_0(t, k, X))^2] + \mathbb{E}_{P_0} [(F_0(t, k, X) - \mathbf{1}\{\eta(t) = k\})^2],
\end{aligned}$$

where the last equality follows from the tower property. Hence, using Fubini, we have

$$P[\bar{B}_\tau(F, \cdot)] = \|F - F_0\|_{P_0}^2 + P_0[\bar{B}_\tau(F_0, \cdot)]. \quad \square$$

Proof of Proposition 6.1. The result follows from Lemma A.1. \square

In the following, let Θ denote the function space consisting of all conditional state occupation probability functions for some measure P as defined in equation (5).

Proof of Corollary 6.2. First note that minimising the loss \bar{B}_τ is equivalent to minimising the loss $\bar{B}_{\tau,0}$, so the discrete super learner and oracle according to \bar{B}_τ and $\bar{B}_{\tau,0}$ are identical. By Lemma A.1, $R_0(F) \geq 0$ for any $F \in \Theta$, and so using Theorem 2.3 from [van der Vaart et al., 2006] with $p = 1$, we have that for all $\delta > 0$,

$$\begin{aligned}
\mathbb{E}_{P_0} [R_0(\hat{\varphi}_n(\mathcal{D}_n^{-k}))] &\leq (1 + 2\delta) \mathbb{E}_{P_0} [R_0(\tilde{\varphi}_n(\mathcal{D}_n^{-k}))] \\
&\quad + (1 + \delta) \frac{16K}{n} \log(1 + |\mathcal{F}_n|) \sup_{F \in \Theta} \left\{ M(F) + \frac{v(F)}{R_0(F)} \left(\frac{1}{\delta} + 1 \right) \right\}
\end{aligned}$$

where for each $F \in \Theta$, $(M(F), v(F))$ is some Bernstein pair for the function $o \mapsto \bar{B}_{\tau,0}(F, o)$. As $\bar{B}_{\tau,0}(F, \cdot)$ is uniformly bounded by τ for any $F \in \Theta$, it follows from section 8.1 in [van der Vaart et al., 2006] that $(\tau, 1.5P_0[\bar{B}_{\tau,0}(F, \cdot)^2])$ is a Bernstein pair for $\bar{B}_{\tau,0}(F, \cdot)$. Now, for any $a, b, c \in \mathbb{R}$ we have

$$\begin{aligned}
(a - c)^2 - (b - c)^2 &= (a - b + b - c)^2 - (b - c)^2 \\
&= (a - b)^2 + (b - c)^2 + 2(b - c)(a - b) - (b - c)^2 \\
&= (a - b) \{ (a - b) + 2(b - c) \} \\
&= (a - b) \{ a + b - 2c \},
\end{aligned}$$

so using this with $a = F(t, k, x)$, $b = F_0(t, k, x)$, and $c = \mathbf{1}\{\eta(t) = k\}$, we have by Jensen's inequality

$$\begin{aligned}
& P_0[\bar{B}_{\tau,0}(F, \cdot)^2] \\
&\leq 2\tau \mathbb{E}_{P_0} \left[\sum_{k=0}^3 \int_0^\tau \left\{ (F(t, k, X) - \mathbf{1}\{\eta(t) = k\})^2 - (F_0(t, k, X) - \mathbf{1}\{\eta(t) = k\})^2 \right\}^2 dt \right] \\
&= 2\tau \mathbb{E}_{P_0} \left[\sum_{k=0}^3 \int_0^\tau (F(t, k, X) - F_0(t, k, X))^2 \right. \\
&\quad \left. \times \{ F(t, k, X) + F_0(t, k, X) - 2\mathbf{1}\{\eta(t) = k\} \}^2 dt \right] \\
&\leq 8\tau \mathbb{E}_{P_0} \left[\sum_{k=0}^3 \int_0^\tau (F(t, k, X) - F_0(t, k, X))^2 dt \right] \\
&= 8\tau \|F - F_0\|_{P_0}^2.
\end{aligned}$$

Thus when $v(F) = 1.5P_0[\bar{B}_{\tau,0}(F, \cdot)^2]$ we have by Lemma A.1

$$\frac{v(F)}{R_0(F)} = 1.5 \frac{P_0[\bar{B}_{\tau,0}(F, \cdot)^2]}{P_0[\bar{B}_{\tau,0}(F, \cdot)]} \leq 12\tau,$$

and so using the Bernstein pairs $(\tau, 1.5P_0[\bar{B}_{\tau,0}(F, \cdot)^2])$ we have

$$\sup_{F \in \Theta} \left\{ M(F) + \frac{v(F)}{R_0(F)} \left(\frac{1}{\delta} + 1 \right) \right\} \leq \tau \left(13 + \frac{12}{\delta} \right),$$

For all $\delta > 0$ we thus have

$$\begin{aligned} \mathbb{E}_{P_0} [R_0(\hat{\varphi}_n(\mathcal{D}_n^{-k}))] &\leq (1 + 2\delta) \mathbb{E}_{P_0} [R_0(\tilde{\varphi}_n(\mathcal{D}_n^{-k}))] \\ &\quad + (1 + \delta) \log(1 + |\mathcal{F}_n|) \tau \frac{16K}{n} \left(13 + \frac{12}{\delta} \right), \end{aligned}$$

and then the final result follows from Lemma A.1. \square

Proof of Corollary 6.3. By definition of the oracle and Lemma A.1, $\mathbb{E}_{P_0} [\|\tilde{\varphi}_n(\mathcal{D}_n^{-k}) - F_0\|_{P_0}^2] \leq \mathbb{E}_{P_0} [\|\varphi_n(\mathcal{D}_n^{-k}) - F_0\|_{P_0}^2]$ for all $n \in \mathbb{N}$. The results then follows from Corollary 6.2. \square

B The state learner with targeted learning

In this section show that a product structure is preserved when the estimator $\bar{\Psi}(\hat{F}_n, \hat{H}_n)$ is used instead of $\tilde{\Psi}(\hat{\Lambda}_n, \hat{\Gamma}_n, \hat{H}_n)$.

Proof of Proposition 6.4. For notational convenience we suppress X in the following. The final result can be obtained by adding the argument X to all functions and averaging. We use the relations from equation (8) to write

$$\begin{aligned} &\int_0^\tau w(s) \left\{ \Gamma(s) - \hat{\Gamma}_n(s) \right\} [\Lambda - \hat{\Lambda}_n](ds) \\ &= \int_0^\tau w(s) \left\{ \int_0^s \frac{F(du, 2)}{F(u-, 0)} - \int_0^s \frac{\hat{F}_n(du, 2)}{\hat{F}_n(u-, 0)} \right\} \left[\frac{F(ds, 1)}{F(s-, 0)} - \frac{\hat{F}_n(ds, 1)}{\hat{F}_n(s-, 0)} \right] \\ &= \int_0^\tau w(s) \left\{ \int_0^s \left(\frac{1}{F(u-, 0)} - \frac{1}{\hat{F}_n(u-, 0)} \right) F(du, 2) \right. \\ &\quad \left. + \int_0^s \frac{1}{\hat{F}_n(u-, 0)} [F(du, 2) - \hat{F}_n(du, 2)] \right\} \\ &\quad \times \left[\left(\frac{1}{F(s-, 0)} - \frac{1}{\hat{F}_n(s-, 0)} \right) F(ds, 1) + \frac{1}{\hat{F}_n(s-, 0)} (F(ds, 1) - \hat{F}_n(ds, 1)) \right] \\ &= \int_0^\tau \int_0^s w(s) \left(\frac{1}{F(u-, 0)} - \frac{1}{\hat{F}_n(u-, 0)} \right) \left(\frac{1}{F(s-, 0)} - \frac{1}{\hat{F}_n(s-, 0)} \right) F(du, 2) F(ds, 1) \\ &\quad + \int_0^\tau \int_0^s w(s) \left(\frac{1}{F(u-, 0)} - \frac{1}{\hat{F}_n(u-, 0)} \right) \frac{F(du, 2)}{\hat{F}_n(u-, 0)} (F(ds, 1) - \hat{F}_n(ds, 1)) \\ &\quad + \int_0^\tau \int_0^s \frac{w(s)}{\hat{F}_n(u-, 0)} [F(du, 2) - \hat{F}_n(du, 2)] \left(\frac{1}{F(s-, 0)} - \frac{1}{\hat{F}_n(s-, 0)} \right) F(ds, 1) \\ &\quad + \int_0^\tau \int_0^s \frac{w(s)}{\hat{F}_n(u-, 0)} [F(du, 2) - \hat{F}_n(du, 2)] \frac{1}{\hat{F}_n(s-, 0)} (F(ds, 1) - \hat{F}_n(ds, 1)). \end{aligned}$$

Consider the first term on the right hand side. Defining

$$w_n^*(t) = \left(F(t-, 0) - \hat{F}_n(t-, 0) \right) \left(\frac{1}{F(t-, 0)} - \frac{1}{\hat{F}_n(t-, 0)} \right),$$

we can write

$$\begin{aligned} & \int_0^\tau \int_0^s w(s) \left(\frac{1}{F(u-, 0)} - \frac{1}{\hat{F}_n(u-, 0)} \right) \left(\frac{1}{F(s-, 0)} - \frac{1}{\hat{F}_n(s-, 0)} \right) F(du, 2) F(ds, 1) \\ &= \int_0^\tau \int_0^s w(s) w_n^*(u) \left(F(u-, 0) - \hat{F}_n(u-, 0) \right) \\ & \quad \times w_n^*(s) \left(F(s-, 0) - \hat{F}_n(s-, 0) \right) F(du, 2) F(ds, 1) \\ &= \int_0^\tau \int_0^s w_n^a(s, u) \left(F(u-, 0) - \hat{F}_n(u-, 0) \right) \left(F(s-, 0) - \hat{F}_n(s-, 0) \right) F(du, 2) F(ds, 1), \end{aligned}$$

where we have defined $w_n^a(s, u) = w(s) w_n^*(s) w_n^*(u)$. By assumption, $w_n^a(s, u)$ is uniformly bounded. The same approach can be applied to the three remaining terms which gives the result. \square

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