

# 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. In right-censored data, the choice of the loss function and the estimation of the expected loss need careful consideration. We introduce the state learner, a new super learner for survival analysis, which simultaneously evaluates libraries of prediction models for the event of interest and the censoring distribution. The state learner places no restrictions on the algorithms that can be included in the library, works in the presence of competing risks, and does not require a single pre-specified estimator of the conditional censoring distribution. We establish an oracle inequality for the state learner and investigate its performance through numerical experiments. We illustrate the application of the state learner with prostate cancer data.

**Keywords:** *Competing risks, cross-validation, loss based estimation, right-censored data, super learner*

## 1 Introduction

Accurate risk prediction from time-to-event data is an important problem in many areas of medical research and public health. Super learning [van der Laan et al., 2007], also known as ensemble learning or stacked regression [Wolpert, 1992, Breiman, 1996], provides a powerful approach to this problem by combining multiple candidate prediction models. In the context of survival analysis, a super learner can for instance combine Cox regression models and random survival forests [Gerds and Kattan, 2021, Section 8.4].

In this paper we propose the state learner, a new super learner designed to handle the specific challenges of ensemble learning with right-censored data. The state learner estimates the performance of a library of candidate models for both the event-time and censoring distributions simultaneously. This joint estimation framework avoids the need for pre-specifying a censoring model, which is a limitation of many existing methods. Our approach also allows for full flexibility in the choice of models in the library, contrasting with earlier proposals that restrict the library to specific model classes [Polley and van der Laan, 2011, Golmakani and Polley, 2020]. Furthermore, unlike iterative approaches such as those in Han et al. [2021] and Westling et al. [2021], we can provide theoretical guarantees for the performance of the state learner.

The state learner is based on the simple idea of considering right-censored competing risks data as an artificial multi-state system where censoring is included as a state of its own. Candidate models are then assessed based on how well they predict the state occupations of this system across time, based on baseline covariate information. We demonstrate how to construct a library for the state learner using existing survival models, and how to obtain risk predictions from the resulting ensemble. To analyse the theoretical properties of the state learner we focus on the discrete super learner which picks the model in the library with best estimated performance [van der Laan et al., 2007]. We show that the discrete state learner is consistent under natural conditions and prove a finite-sample oracle inequality.

## 1.1 Related work

Super learning requires a library of candidate models, or *learners*, and a loss function for evaluating performance on hold-out samples. Machine learning based on right-censored data commonly uses the partial log-likelihood as a 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]. This loss function is also suggested for super learning with right-censored data by Polley and van der Laan [2011], where data is assumed to be observed in discrete time. However, the partial log-likelihood loss does not work well as a measure of performance in hold-out samples observed in continuous time. The reason is that the partial log-likelihood loss assigns an infinite value for any learner that predicts piece-wise constant cumulative hazard functions when there are event times in the test set which do not occur in the learning set. This problem occurs with prominent survival learners including the Kaplan-Meier estimator, random survival forests, and semi-parametric Cox regression models and these learners cannot be included in the library of the super learner proposed by Polley and van der Laan [2011]. When a proportional hazards model is assumed, the baseline hazard function can be profiled out of the likelihood [Cox, 1972]. The cross-validated partial log-likelihood loss [Verweij and van Houwelingen, 1993] has therefore been suggested as a loss function for super learning by Golmakani and Polley [2020]. This choice of loss function restricts the library of learners to include only Cox proportional hazards models, and hence excludes many learners such as, e.g., random survival forests, additive hazards models, and accelerated failure time models.

Alternative approaches for super learning with right-censored data use an inverse probability of censoring weighted (IPCW) loss function [Graf et al., 1999, van der Laan and Dudoit, 2003, Molinaro et al., 2004, Keles et al., 2004, Hothorn et al., 2006, Gerds and Schumacher, 2006, Gonzalez Ginestet et al., 2021], censoring unbiased transformations [Fan and Gijbels, 1996, Steingrimsson et al., 2019], or pseudo-values [Andersen et al., 2003, Mogensen 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.

More recent work by Han et al. [2021] and Westling et al. [2021] circumvents the need to pre-specify a censoring model by iterating between estimation of the outcome and censoring models. However, it seems that this procedure is in general not guaranteed to converge to the true data-generating mechanism [Munch, 2024, Appendix A.4].

## 1.2 Outline of the paper

We introduce our notation and framework in Section 2. Section 3 defines general super learning for right-censored data. In Section 4 we define the state learner, while Section 5 provides theoretical guarantees. In Section 6 we demonstrate how the state learner can be

used to obtain risk predictions and how it can be applied in the context of causal inference. Section 7 reports the results of numerical experiments, and Section 8 illustrates the method on prostate cancer data. We conclude with a discussion in Section 9. Proofs are collected in Appendix A. Code and an implementation of the state learner are available at <https://github.com/ammudn/statelearner>.

## 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 prediction horizon. 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  $\Lambda_j: [0, \tau] \times \mathcal{X} \rightarrow \mathbb{R}_+$  are defined as

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

For ease of presentation we assume throughout that the map  $t \mapsto \Lambda_j(t | x)$  is continuous for all  $x$  and  $j$ . All arguments carry over directly to the general case. 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  $\mathcal{M}_\tau$  denote the space of all conditional cumulative hazard functions on  $[0, \tau] \times \mathcal{X}$ . Any distribution  $Q \in \mathcal{Q}$  can be characterised by

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

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

We consider the right-censored setting in which we observe  $O = (\tilde{T}, \tilde{D}, X)$ , where  $\tilde{T} = \min(T, C)$  for a right-censoring time  $C$ ,  $\Delta = \mathbf{1}\{T \leq C\}$ , 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 times and the censoring times are conditionally independent given covariates,  $T \perp\!\!\!\perp C | X$ . This implies that any distribution  $P \in \mathcal{P}$  is characterised 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  $\Gamma \in \mathcal{M}_\tau$  to denote the conditional cumulative hazard function for censoring. For ease of presentation we now also assume that  $\Gamma(\cdot | x)$  is continuous for all  $x$ . We let  $(t, x) \mapsto G(t | x) = \exp \{-\Gamma(t | x)\}$  denote the survival function of the conditional censoring distribution. The distribution  $P$  is characterised by

$$P(dt, j, dx) = \{G(t- | x)S(t- | x)\Lambda_1(dt | x)H(dx)\}^{\mathbf{1}\{j=1\}} \\ \{G(t- | x)S(t- | x)\Lambda_2(dt | x)H(dx)\}^{\mathbf{1}\{j=2\}} \\ \{G(t- | x)S(t- | x)\Gamma(dt | x)H(dx)\}^{\mathbf{1}\{j=0\}} \quad (2) \\ = \{G(t- | x)Q(dt, j, dx)\}^{\mathbf{1}\{j \neq 0\}} \\ \{G(t- | x)S(t- | x)\Gamma(dt | x)H(dx)\}^{\mathbf{1}\{j=0\}}.$$

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

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

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

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

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

Thus, we can consider  $\Lambda_j$  and  $\Gamma$  as operators which map from  $\mathcal{P}$  to  $\mathcal{M}_\tau$ .

### 3 Super learning

In survival analysis, a super learner can be used to estimate a parameter  $\theta \in \Theta$  which can be identified from the observed data distribution  $P \in \mathcal{P}$ . A super learner typically estimates a function, and thus the parameter space  $\Theta$  is most often a class of functions. For example,  $\theta$  could be a conditional survival function or a cumulative hazard function. In Section 4 we consider a specific choice of parameter as target for our super learner, but in this section we describe super learning for a general parameter  $\theta$  with values in some parameter space  $\Theta$ .

As input to a super learner we need a data set  $\mathcal{D}_n = \{O_i\}_{i=1}^n$  of i.i.d. observations from  $P \in \mathcal{P}$  and a collection of candidate models or learners  $\mathcal{A}$ . Each learner  $a \in \mathcal{A}$  is a map  $a: \mathcal{O}^n \rightarrow \Theta$  which takes a data set as input and returns an estimate  $a(\mathcal{D}_n) \in \Theta$  of  $\theta$ . In what follows, we use the short-hand notation  $P[f] = \int f(o)P(do)$ . A super learner evaluates the performance of  $a \in \mathcal{A}$  with a loss function  $L: \Theta \times \mathcal{O} \rightarrow \mathbb{R}_+$  and estimates 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 oracle learner is defined as the learner that minimises the expected loss under the data-generating distribution  $P$ , i.e.,

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

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. However, these dependencies are suppressed in the notation.

## 4 The state learner

The main idea of the state learner is to jointly use learners for  $\Lambda_1$ ,  $\Lambda_2$ , and  $\Gamma$ , 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 for the tuple of the cumulative hazard functions  $(\Lambda_1, \Lambda_2, \Gamma)$  based on how well they jointly model the observed data. To formally introduce the state learner, we define the artificial multi-state process

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

We use the phrase ‘artificial’ because multi-state models should not usually include censoring as a state. At time  $t$ , we observe that each individual is in one of four mutually exclusive states: 0, 1, 2, or  $-1$ . The conditional distribution of the process  $\eta(t)$  given baseline covariates  $X$  is determined by the function

$$F(t, k, x) = P(\eta(t) = k \mid X = x), \quad (5)$$

for all  $t \in [0, \tau]$ ,  $k \in \{-1, 0, 1, 2\}$ , and  $x \in \mathcal{X}$ . The function  $F$  describes the conditional state occupation probabilities of the process  $\eta$ .

We define the state learner as a super learner for the function-valued parameter  $\theta(P) = F$  which is identified through equation (5). Under conditional independent censoring each tuple  $(\Lambda_1, \Lambda_2, \Gamma, H)$  characterises a distribution  $P \in \mathcal{P}$ , c.f. equation (2), which in turn determines  $(F, H)$ . Hence, a learner for  $F$  can be constructed from learners for  $\Lambda_1$ ,  $\Lambda_2$ , and  $\Gamma$  as follows:

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

Equation (6) implies that a library for the state learner can be build from three libraries of learners:  $\mathcal{A}_1$ ,  $\mathcal{A}_2$ , and  $\mathcal{B}$ , where  $\mathcal{A}_1$  and  $\mathcal{A}_2$  contain learners for the conditional cause-specific cumulative hazard functions  $\Lambda_1$  and  $\Lambda_2$ , respectively, and  $\mathcal{B}$  contains learners for 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  $\mathcal{F}$  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 correspondence with the relations in equation (6),

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

Importantly, the libraries  $\mathcal{A}_1$ ,  $\mathcal{A}_2$ , and  $\mathcal{B}$  can be constructed using standard survival analysis software.

To evaluate how well a function  $F$  predicts an observed process  $\eta$  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  $t \in [0, \tau]$ ,

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

Based on a split of a data set  $\mathcal{D}_n$  into  $K$  disjoint approximately equally sized subsets (c.f., 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 given by

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

## 5 Theoretical results for the state learner

In this section we establish theoretical guarantees for the state learner. We show that the state learner is consistent if its library contains a consistent learner, and we establish a finite sample inequality for the excess risk of the state learner compared to the oracle.

### 5.1 Consistency

The following result 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 minimise the average loss of the integrated Brier score, we recover the parameters of the data-generating distribution. Specifically, this implies that the oracle of a state learner is 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  $F_P$  for the function determined by a given  $P \in \mathcal{P}$  in accordance with equation (5). In the following we let  $\mathcal{H}_\mathcal{P} = \{F_P : P \in \mathcal{P}\}$ .

**Proposition 5.1.** *If  $P \in \mathcal{P}$  then*

$$F_P = \underset{F \in \mathcal{H}_\mathcal{P}}{\operatorname{argmin}} P[\bar{B}_\tau(F, \cdot)],$$

*$P$ -almost surely.*

*Proof.* See Appendix A.1. □

### 5.2 Oracle inequalities

We establish a finite sample oracle result for the state learner. Our Proposition 5.2 is in essence a special case of Theorem 2.3 in [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 emphasise the dependence on  $n$ . In the following we let the space  $\mathcal{H}_{\mathcal{P}}$  be equipped with the norm  $\|\cdot\|_P$  defined as

$$\|F\|_P = \left\{ \sum_{j=-1}^2 \int_{\mathcal{X}} \int_0^\tau F(t, j, x)^2 dt P(dx) \right\}^{1/2}. \quad (7)$$

**Proposition 5.2.** *For all  $P \in \mathcal{P}$ ,  $n \in \mathbb{N}$ ,  $k \in \{1, \dots, K\}$ , and  $\delta > 0$ ,*

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

*Proof.* See Appendix A.2. □

Proposition 5.2 has the following asymptotic consequences.

**Corollary 5.3.** *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  $\mathbb{E}_P [\|\varphi_n(\mathcal{D}_n^{-k}) - F_P\|_P^2] = O(n^{-\alpha})$ , for some  $\alpha \leq 1$ .*

- (a) *If  $\alpha = 1$  then  $\mathbb{E}_P [\|\hat{\varphi}_n(\mathcal{D}_n^{-k}) - F_P\|_P^2] = O(\log(n)n^{-1})$ .*
- (b) *If  $\alpha < 1$  then  $\mathbb{E}_P [\|\hat{\varphi}_n(\mathcal{D}_n^{-k}) - F_P\|_P^2] = O(n^{-\alpha})$ .*

*Proof.* See Appendix A.2. □

Proposition 5.2 provides a precise bound on the average price we pay for using cross-validation to select a learner from a library of candidates as compared to knowing the oracle learner in advance. Corollary 5.3 states that this price is asymptotically vanishing as long as the number of learners in the library grows with sample size at a polynomial rate.

## 6 Use cases for the state learner

The state learner estimates the parameter  $F$  which is a feature of the observed right-censored data distribution  $P$ . In particular,  $F$  depends on the censoring distribution and is typically not of direct interest in itself. In the following, we describe how an estimate of  $F$ , as provided by the state learner, can be used to estimate more relevant parameters of interest, such as, e.g., survival probabilities.

### 6.1 Survival and risk predictions

Event-free survival probabilities and risk predictions can be obtained from the state-occupation function  $F$  under the assumption of conditional independent censoring and positivity, as introduced in Section 2. By equations (3) and (4) and the definition of  $F$ , we have

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

Equation (1) provides a formula for obtaining event-free survival probabilities from the cause-specific cumulative hazard functions. Similarly, cause-specific risk predictions can be obtained from  $\Lambda_1$  and  $\Lambda_2$  using the formula [e.g., Benichou and Gail, 1990, Ozenne et al., 2017],

$$Q(T \leq t, D = j \mid X = x) = \int_0^t \exp \{-\Lambda_1(u \mid x) - \Lambda_2(u \mid x)\} \Lambda_j(du \mid x), \quad j \in \{1, 2\}. \quad (9)$$

Hence, given the state learner’s estimate of  $F$  we can use equation (8) to obtain estimates of the cause-specific cumulative hazard functions  $\Lambda_j$ , which can in turn be used to obtain estimates of the event-free survival probabilities and cause-specific risks through equations (1) and (9).

In Section 4 we suggested to implement the state learner by building a library using learners of the cause-specific cumulative hazard functions,  $\Lambda_j$ , and the cumulative hazard function for censoring,  $\Gamma$ . With this implementation we can directly input the highest ranked tuple of cause-specific hazard functions  $(\Lambda_1, \Lambda_2)$  provided by the state learner as input to equations (1) and (9).

## 6.2 Targeted and debiased machine learning

The framework of *targeted* or *debiased* machine learning is a general methodology for combining data-adaptive modeling, such as machine and super learning, with asymptotically valid statistical inference for interpretable target parameters [van der Laan and Rubin, 2006, Chernozhukov et al., 2018]. This framework has been applied extensively for causal inference based on observational data [e.g., van der Laan and Rose, 2011, Kennedy, 2016, Rytgaard and van der Laan, 2022]. A targeted or debiased estimator is constructed by first estimation high-dimensional nuisance parameters using machine learning, and then employing a debiasing or targeting step by using tools from semi-parametric efficiency theory [Pfanzagl and Wefelmeyer, 1982, Bickel et al., 1993, van der Laan and Robins, 2003, Tsiatis, 2007, Kennedy, 2022]. In the context of right-censored competing risk data, the high-dimensional nuisance parameters needed to be estimated will typically include the cause-specific cumulative hazard functions and the cumulative hazard function for censoring [e.g., van der Laan and Robins, 2003, Rytgaard et al., 2021, Rytgaard and van der Laan, 2022]. The state learner is hence particularly well suited for targeted and debiased machine learning as it immediately provides estimates of these nuisance parameters. Though it served as our original motivation for developing the state learner, we leave the study of the state learner in the context of targeted and debiased machine learning for a future paper.

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## 7 Numerical experiments

In this section we report results from a simulation study where we consider estimation of the conditional survival function. In the first part, we compare the state learner to two IPCW based discrete super learners that use either the Kaplan-Meier estimator or a Cox model to estimate the censoring probability [Gonzalez Ginestet et al., 2021]. In the second part we compare the state learner to the super learner proposed by Westling et al. [2021].

In both parts we use the same data-generating mechanism. We generate data according to a distribution motivated from a real data set in which censoring depends on the baseline covariates. We simulate data based on the prostate cancer study of Kattan et al. [2000]. The outcome of interest is the time to tumor recurrence, and five baseline covariates are 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 implies that the time of censoring depends on the radiation dose. The data were re-analysed in [Gerds et al., 2013] where a sensitivity analysis was conducted based on simulated data. Here 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 distribution and the censoring distribution. Note that the three learners in our library of learners can be used to learn the cumulative hazard functions of the outcome and the censoring distribution. The latter works by training the learner on the data set  $\mathcal{D}_n^c$ , where  $\mathcal{D}_n^c = \{O_i^c\}_{i=1}^n$  with  $O_i^c = (\tilde{T}_i, 1 - \Delta_i, X_i)$ . 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 compare the state learner to two IPCW based super learners: The first super learner, called IPCW(Cox), uses a Cox model with main effects to estimate the censoring probabilities, while the second super learner, called IPCW(KM), uses the Kaplan-Meier estimator to estimate the censoring probabilities. 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]. The IPCW super learners use the integrated Brier score up to a fixed time horizon (36 months). The marginal risk of the event before this time horizon is  $\approx 24.6\%$ . Under the ‘dependent censoring’ setting the marginal censoring probability before the time horizon is  $\approx 61.9\%$ . Under the ‘independent censoring’ setting the marginal censoring probability before this time horizon is  $\approx 38.7\%$ .

Each super learner provides a learner for the cumulative hazard function for the outcome of interest. From the cumulative hazard function a risk prediction model can be obtained as described in Section 6.1 (with the special case of  $\Lambda_2 = 0$ ). We measure the 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 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, which uses the large data set of uncensored event times to select the learner with the highest IPA.

The results are shown in Figure 1. We see that in the scenario where censoring depends on the covariates, 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

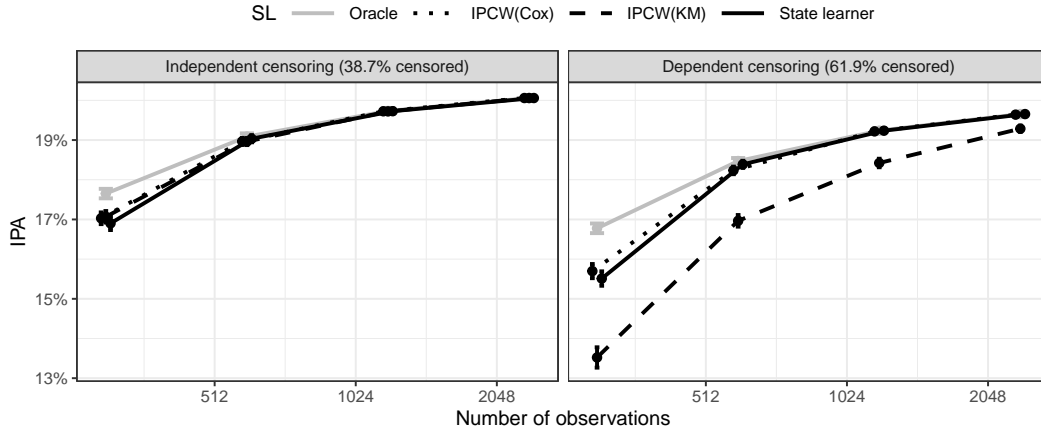


Figure 1: For the risk prediction models provided by each of the super learners, the IPA is plotted against sample size. The results are averages across 1000 simulated data sets and the error bars are used to quantify the Monte Carlo uncertainty.

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]. This is another super learner which like the state learner works without a pre-specified censoring model. Note that both the state learner and `survSL` provide a prediction model for the event time outcome and also for the probability of being censored. Hence, we compare the performance of these methods with respect to both the outcome and the censoring distribution. Again we use the IPA to quantify the predictive performance.

The results are shown in Figures 2 and 3. We see that for most sample sizes, the state learner selected prediction models for both censoring and outcome which have similar or higher IPA compared to the prediction models selected by `survSL`.

## 8 Prostate cancer study

In this section we use the prostate cancer data of Kattan et al. [2000] to illustrate the use of the state learner in the presence of competing risks. We have introduced the data in Section 7. The data consists of 1,042 patients who are followed from start of followup until tumor recurrence, death without tumor recurrence or end of followup (censored) whatever came first. We use the state learner to rank libraries of learners for the cause-specific cumulative hazard functions of tumor recurrence, death without tumor recurrence, and censoring. The libraries of learners each include five learners: the Nelson-Aalen estimator, three Cox regression models (unpenalized, Lasso, Elastic net) each including additive effects of the 5 covariates (c.f., Section 7), and a random survival forest. We use the same set of learners to learn the cumulative hazard function of tumor recurrence  $\Lambda_1$ , the cumulative hazard function of death without tumor recurrence  $\Lambda_2$ , and the cumulative hazard function of the conditional censoring distribution  $\Gamma$ .

This gives a library consisting of  $5^3 = 125$  learners for the conditional state occupation

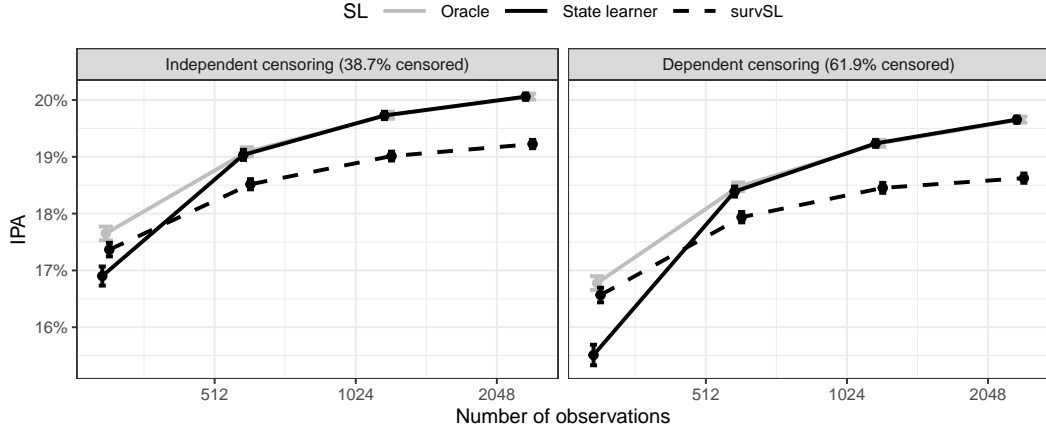


Figure 2: For the risk prediction models of the outcome provided by each of the super learners, the IPA at the fixed time horizon is plotted against sample size. The results are averages across 1000 repetitions and the error bars are used to quantify the Monte Carlo uncertainty.

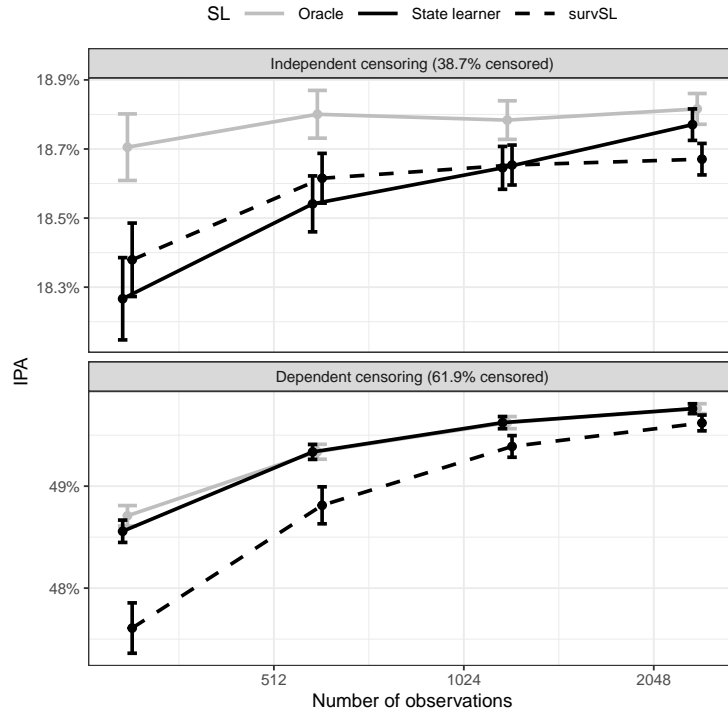


Figure 3: For the risk prediction models of the censoring model provided by each of the super learners, the IPA at the fixed time horizon is plotted against sample size. The results are averages across 1000 repetitions and the error bars are used to quantify the Monte Carlo uncertainty.

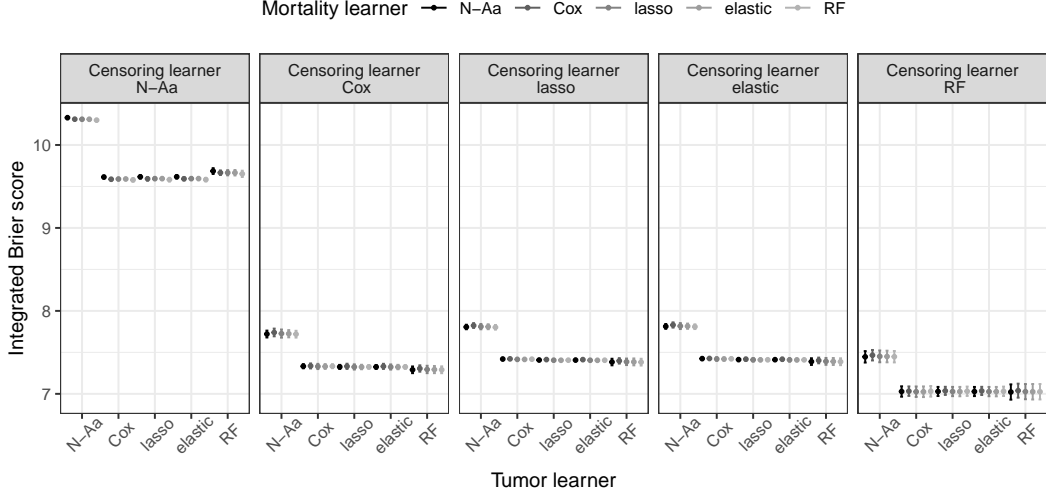


Figure 4: The results of applying the 125 combinations of learners to the prostate cancer data set. The error bars are based on five repetitions using different splits. We refer to learners of  $\Lambda_1$ ,  $\Lambda_2$ , and  $\Gamma$  as ‘Tumor learner’, ‘Mortality learner’, and ‘Censoring learner’, respectively.

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 4) for all learners are shown in Figure 4. 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.

## 9 Discussion

The state learner is a new super learner that can be used with right-censored data and competing events. Compared to existing IPCW-based 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 a library of candidate learners. Furthermore, the state learner neither requires that the cause-specific cumulative hazard functions  $\Lambda_j$  can be written as integrals with respect to Lebesgue measure, nor does it assume a (semi)parametric formula. In the remainder of this section we discuss the limitations of our proposal and avenues for further research.

A major advantage of the state learner is that the performance of each combination of learners can be estimated without additional nuisance parameters. A potential drawback of our approach is that we are evaluating the loss of the learners on the level of the observed data distribution while the target of the analysis is either the event time distribution, or the censoring distribution, or both. Specifically, the finite sample oracle inequality in Proposition 5.2 concerns the function  $F$ , which is a feature of  $P \in \mathcal{P}$ , while what we are typically interested in is  $\Lambda_j$  or  $S$ , which are features of  $Q \in \mathcal{Q}$ . We emphasise that while the state learner provides us with estimates of  $\Lambda_j$  and  $\Gamma$  based on libraries  $\mathcal{A}_j$  and  $\mathcal{B}$ , the performance of these learners is not assessed directly for their respective target parameters, but only indirectly via the performance of  $F$ . For settings without competing risks, our numerical studies suggest that measuring the performance of  $F$  also leads to good performance for

estimation of  $S$ .

Our proposed super learner can be implemented with a broad library of learners and using existing software. Furthermore, while the library  $\mathcal{F}(\mathcal{A}_1, \mathcal{A}_2, \mathcal{B})$  consists of  $|\mathcal{A}_1||\mathcal{A}_2||\mathcal{B}|$  many learners, we only need to fit  $|\mathcal{A}_1| + |\mathcal{A}_2| + |\mathcal{B}|$  many learners in each fold. To evaluate the performance of each learner we need to perform  $|\mathcal{A}_1||\mathcal{A}_2||\mathcal{B}|$  many 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 not more computationally demanding than any procedure that uses super learning to learn  $\Lambda_1$ ,  $\Lambda_2$ , and  $\Gamma$  separately. While our proposal is based on constructing the library  $\mathcal{F}$  from libraries for learning  $\Lambda_1$ ,  $\Lambda_2$ , and  $\Gamma$ , it could also be of interest to consider learners that estimate  $F$  directly.

In our numerical studies, we only considered learners of  $\Lambda_j$  and  $\Gamma$  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  $\Lambda_j$  or  $\Gamma$  are absolutely continuous in the time argument, calculating  $F$  is more involved, but we expect that a good approximation can be achieved by discretisation.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## A Proofs

This section contains proofs of the results stated in the paper. Section A.1 contains a proof of the consistency result from Section 5.1, and Section A.2 contains proofs of the oracle inequalities from Section 5.2.



## A.1 Consistency

Define  $\bar{B}_{\tau,P}(F, o) = \bar{B}_\tau(F, o) - \bar{B}_\tau(F_P, o)$  and  $R_P(F) = P[\bar{B}_{\tau,P}(F, \cdot)]$ , where the integrated Brier score  $\bar{B}_\tau$  was defined in Section 4. Recall the norm  $\|\cdot\|_P$  defined in equation (7).

**Lemma A.1.**  $R_P(F) = \|F - F_P\|_P^2$ .

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

$$\begin{aligned} & \mathbb{E}_P [(F(t, j, X) - \mathbb{1}\{\eta(t) = j\})^2] \\ &= \mathbb{E}_P [(F(t, j, X) - F_P(t, j, X) + F_P(t, j, X) - \mathbb{1}\{\eta(t) = j\})^2] \\ &= \mathbb{E}_P [(F(t, j, X) - F_P(t, j, X))^2] + \mathbb{E}_P [(F_P(t, j, X) - \mathbb{1}\{\eta(t) = j\})^2] \\ &\quad + 2\mathbb{E}_P [(F(t, j, X) - F_P(t, j, X))(F_P(t, j, X) - \mathbb{1}\{\eta(t) = j\})] \\ &= \mathbb{E}_P [(F(t, j, X) - F_P(t, j, X))^2] + \mathbb{E}_P [(F_P(t, j, X) - \mathbb{1}\{\eta(t) = j\})^2], \end{aligned}$$

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

$$P[\bar{B}_\tau(F, \cdot)] = \|F - F_P\|_P^2 + P[\bar{B}_\tau(F_P, \cdot)].$$

□

*Proof of Proposition 5.1.* The result follows from Lemma A.1. □

## A.2 Oracle inequalities

Recall that we use  $\mathcal{F}_n$  to denote a library of learners for the function  $F$ , and that  $\hat{\varphi}$  and  $\tilde{\varphi}$  denotes, respectively, the discrete super learner and the oracle learner for the library  $\mathcal{F}_n$ , c.f., Section 4.

*Proof of Proposition 5.2.* First note that minimising the loss  $\bar{B}_\tau$  is equivalent to minimising the loss  $\bar{B}_{\tau,P}$ , so the discrete super learner and oracle according to  $\bar{B}_\tau$  and  $\bar{B}_{\tau,P}$  are identical. By Lemma A.1,  $R_P(F) \geq 0$  for any  $F \in \mathcal{H}_P$ , and so using Theorem 2.3 from [van der Vaart et al., 2006] with  $p = 1$ , we have that for all  $\delta > 0$ ,

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

where for each  $F \in \mathcal{H}_P$ ,  $(M(F), v(F))$  is some Bernstein pair for the function  $o \mapsto \bar{B}_{\tau,P}(F, o)$ . As  $\bar{B}_{\tau,P}(F, \cdot)$  is uniformly bounded by  $\tau$  for any  $F \in \mathcal{H}_P$ , it follows from section 8.1 in [van der Vaart et al., 2006] that  $(\tau, 1.5P[\bar{B}_{\tau,P}(F, \cdot)^2])$  is a Bernstein pair for  $\bar{B}_{\tau,P}(F, \cdot)$ . 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  $a = F(t, j, x)$ ,  $b = F_P(t, j, x)$ , and  $c = \mathbb{1}\{\eta(t) = j\}$ , we have by Jensen's inequality

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

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

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

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

$$\sup_{F \in \mathcal{H}_P} \left\{ M(F) + \frac{v(F)}{R_P(F)} \left( \frac{1}{\delta} + 1 \right) \right\} \leq \tau \left( 13 + \frac{12}{\delta} \right).$$

For all  $\delta > 0$  we thus have

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

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

*Proof of Corollary 5.3.* By definition of the oracle and Lemma A.1,

$$\mathbb{E}_P [\|\tilde{\varphi}_n(\mathcal{D}_n^{-k}) - F_P\|_P^2] \leq \mathbb{E}_P [\|\varphi_n(\mathcal{D}_n^{-k}) - F_P\|_P^2]$$

for all  $n \in \mathbb{N}$ . The results then follows from Proposition 5.2.  $\square$