Penalized maximum likelihood for cure regression models

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Abstract

We propose a new likelihood approach for estimation, inference and variable selection for parametric cure regression models in time-to-event analysis under random right-censoring. In such a context, it often happens that some subjects under study are “cured”, meaning that they do not experience the event of interest. Then, the sample of censored observations is an unlabeled mixture of cured and “susceptible” subjects. Using inverse probability censoring weighting (IPCW), we propose a binary outcome regression likelihood for the probability of being cured given the covariate vector. Meanwhile the conditional law of the susceptible subjects is allowed to be very general. The IPCW requires a preliminary fit for the conditional law of the censoring, for which general parametric, semi- or non-parametric approaches could be used. The incorporation of a penalty term in our approach is straightforward; we propose \( \ell_1 \)-type penalties for variable selection. Our theoretical results are derived under mild technical assumptions. Simulation experiments and real data analysis illustrate the effectiveness of the new approach.

Keywords. Adaptive lasso; Inverse probability censoring weighting; iid representation.

MSC 2010 subject classification: 62N01, 62N02, 62J07

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1 Introduction

Standard survival models assume that all individuals experience the event of interest eventually (cf. Kalbfleisch and Prentice (2002)). However, this assumption is not always tenable since, for example, some diseases may require specific biological and/or lifestyle traits in place to activate, or it may be that immunity is a consequence of successful curative treatment (or, indeed, a combination of both treatment and pre-treatment attributes). The individuals who will not experience the event are referred to as cured or non-susceptible, and, although the former is perhaps suggestive of treatment, both are used interchangeably in the biostatistical literature. While there may be scenarios where it is possible to medically examine individuals to determine who is cured, typically the “cure status” is unknown and inference about cure mechanisms is based on the results of a survival study. Note that, as the observation period increases in such a study, the sample becomes composed of relatively more censoring times since the cured individuals never contribute event times. In practice then, the presence of cured individuals can be visualized in terms of the Kaplan-Meier curve (Kaplan and Meier, 1958) which will plateau as time increases (instead of tending towards zero).

The importance of estimating the cured proportion was recognized by Boag (1949) and Berkson and Gage (1952) who made use of a mixture model. Here, the overall survival distribution is improper with mixture components given by: (i) a proper survival distribution for uncured individuals (usually referred to as the latency distribution), and (ii) a point mass at time infinity for cured individuals. Farewell (1977, 1982) extended this work to incorporate covariates in both the latency component (proportional hazards Weibull model) and the cure component (logistic regression model). This mixture model structure permits quite straightforward interpretation and is the most widely used cure model. However other formulations exist, notably the bounded cumulative hazard model (Tsodikov, 1998; Tsodikov et al., 2003), which can be motivated through an underlying mechanistic model for tumor growth, or the compound Poisson multiplicative frailty model (Aalen, 1992; Duchateau and Janssen, 2007), which assigns a zero frailty (and, hence, zero hazard) to a mass of individuals (i.e., cured individuals). Studies concerning mixture cure models can also be traced in the labor economics literature, under the name split population duration models (Schmidt and Witte, 1989), and in the reliability literature under the name limited-failure population models (Meeker, 1987).

While much early work in cure modelling assumed a parametric latency distribution (e.g., Boag (1949) used a log-normal model, and Farewell (1977, 1982) used a Weibull model), non/semi-parametric approaches are typically preferred in the analysis of time-to-event data. Furthermore, Yu et al. (2004) showed that cure estimates can be sensitive to the choice of latency distribution – albeit more flexible parametric cure models are more robust (Peng et al., 1998; Yamaguchi, 1992). The semi-parametric cure model consists of a parametric logistic cure regression component and semi-parametric proportional hazards (PH) (Peng and Dear, 2000; Sy and Taylor, 2000) or accelerated failure time (AFT) latency model (Li and Taylor, 2002; Zhang and Peng, 2007); in both PH and AFT cases,
the baseline latency model is an unspecified function, and estimation is based on the EM algorithm (Dempster et al., 1977) in combination with (modified) partial likelihood (Cox, 1972, 1975) or rank regression (Ritov, 1990; Tsiatis, 1990) respectively. Note that penalized splines have also been considered for the baseline latency model (Corbière et al., 2009). Of course, structural model assumptions are still made in the way that covariates enter (i.e., PH or AFT), and, estimation of the cure component can still be sensitive to such choices.

Our approach differs from the aforementioned. First note that, if the cure status was directly observable, one would simply apply standard binary logistic (or probit) regression. Because, typically, the cure status is not available (e.g., medically or by finite-time survival studies), we propose replacing it with a “proxy” or “synthetic” value, and then proceeding in the usual way. In particular, we generate these synthetic values using inverse probability censoring weighting (IPCW) arguments (Robins and Finkelstein, 2000; van der Laan et al., 2003). This approach obviates the need for a latency model — although IPCW does require estimation of the censoring distribution. At first sight, we trade one missing data framework (EM) for another (IPCW), and latency estimation with censoring estimation. However, in addition to being an interesting new cure estimation process in its own right, our proposal has its advantages. Unlike the existing EM approaches, which are not so easily extended to more flexible latency models (beyond PH and AFT), our general framework does not depend on any particular specification for the censoring model, i.e., this could be very flexible. Furthermore, once the synthetic cure status has been computed (in one initial step), one may avail of standard, fast (GLM) estimation and penalized variable selection procedures thereafter.

The remainder of this article is organized as follows. In Section 2 we introduce a new result which forms the basis of the proposed likelihood estimation procedure of Section 3. In Section 3.2 we present a penalized version of this likelihood for the purpose of variable selection. Asymptotic properties of our estimation procedure are given in Section 4 along with empirical evidence via simulation in Section 5. Real data examples are given in Section 6. We close with some remarks in Section 7. The proofs are postponed to the Appendix.

2 Preliminaries

Let $T \in (0, \infty]$ denote the survival time of interest, and note in particular that, in contrast to standard survival models, the support includes the possibility that $T = \infty$ to allow for cases where the event never occurs, i.e., cured (or non-susceptible) individuals. We also introduce the cure indicator $B = 1(T = \infty) \sim \text{Bernoulli} (\pi)$ so that $\pi$ is the cure probability. Furthermore, $T_0 = T \mid (B = 0)$ is survival time for an uncured individual (the latency time) with survivor function $S_{T_0}(t) = \text{Pr}(T_0 > t)$ whose support is contained in $(0, \infty)$, i.e., $S_{T_0}(t)$ is simply a standard survivor function. Since $\text{Pr}(T > t \mid B) = (1 - B)S_{T_0}(t) + B$, we have that $S_T(t) = \mathbb{E}\{\text{Pr}(T > t \mid B)\} = (1 - \pi)S_{T_0}(t) + \pi$ which is the so-called “mixture cure” model; it is a finite mixture of cured and uncured individuals.
Note that $S_T(\infty) = \pi$ so that, in the time limit (when $\pi > 0$), there is a proportion of individuals who do not experience the event, and $S_T$ has an asymptote.

Generally we will have a vector of covariates, $X$, and it is of particular interest to model the relationship between $X$ and $\pi$. Thus, generalizing the above mixture cure model to covariate dependence, we arrive at

$$S_T(t \mid X) = \left\{1 - \pi(X)\right\}S_{T_0}(t \mid X) + \pi(X)$$

where $\pi(X) = \pi(X; \theta) \in (0, 1]$ is the cure regression function, and $\theta$ is a vector of parameters which describe the relationship between $X$ and the cure probability. Typically, although not necessarily, covariates enter through a linear predictor, i.e., $\pi(X; \theta)$ is a given function of $X^\top \theta$ where $X = (X_{(0)} \equiv 1, X_{(1)}, \ldots, X_{(p)})^\top$ is the covariate vector and $\theta = (\theta_{(0)}, \theta_{(1)}, \ldots, \theta_{(p)})^\top$ is the vector of associated regression coefficients. (Here and in the following, for any matrix $A$, $A^\top$ denotes its transpose.) In our applications, we will make use of a logistic regression function, $\pi(X) = 1/(1 + \exp(-\theta^\top X))$, but one may, of course, use alternative parametric forms (e.g., probit or complementary log-log, or forms in which covariates enter in non-linear ways). Note that we have not suggested any particular model for $S_{T_0}(t \mid X)$ as, in our proposed estimation procedure, this function is completely unspecified.

In the majority of practical applications, we do not observe the cure status, $B$. We observe individuals over a (possibly fixed) time period during which some will experience the event and others will not. Those who do not experience the event during the observation period are censored – but this does not mean they have been cured since they may experience the event at a later stage outside of the observation period. We therefore introduce a censoring time $C \in (0, \infty)$ with survivor function $S_C(t)$. In contrast to $T$, the support of $C$ does not include infinity since, practically, observation windows are finite. Let $Y = T \wedge C$ be the observed time (where $\wedge$ is the minimum operator), and $\Delta = 1(T \leq C) = (1 - B)1(T_0 \leq C)$ is the event indicator. Therefore, due to censoring, neither $T$ nor $B$ are observed so that inference must be made through $Y$ and $\Delta$.

We will assume the following:

$$T_0 \perp C \mid X, \quad (2.1)$$

$$B \perp (T_0, C) \mid X, \quad (2.2)$$

where (2.1) is the standard independence assumption made throughout survival literature, and (2.2) is introduced in the cure context to ensure that the cure regression model is identifiable. In particular, Assumptions (2.1) and (2.2) guarantee that $T \perp C \mid X$. See Lemma 8.1 in the Appendix. With these assumptions in place, it can then be shown that

$$E \left( \frac{\Delta}{S_C(Y - \mid X)} \mid X \right) = E(1 - B \mid X) = 1 - \pi(X) \quad (2.3)$$

where, for any possible value, $x$, of the covariate vector,

$$S_C(t - \mid x) = \Pr(C \geq t \mid X = x).$$
This result is the core of our estimation scheme which is described in Section 3. In fact, (2.3) is a special case of the more general result
\[
\mathbb{E} \left( \frac{\Delta r(Y, X)}{S_C(Y - | X)} \middle| X \right) = \mathbb{E}\{r(T_0, X) \middle| X\} \{1 - \pi(X)\} \tag{2.4}
\]
but with \(r(\cdot, \cdot) = 1\), and, indeed, it is (2.4) which is proved in Lemma 8.2. It is worth highlighting that (2.4) is an application of the Inverse-Probability Censoring Weighting (IPCW) approach (Robins and Finkelstein, 2000) extended to the case where a cured proportion exists; (2.4) reduces to the usual IPCW approach when \(\pi(X) \equiv 0\).

3 Estimation and inference

If the iid replicates of \((B_i, X_i)\) were observed, we would simply have the standard Bernoulli log-likelihood,
\[
\ell(\theta) = \sum_{i=1}^{n} [B_i \log \pi_i(\theta) + (1 - B_i) \log (1 - \pi_i(\theta))], \tag{3.1}
\]
where \(\pi_i(\theta) = \pi(X_i; \theta)\). Of course, (3.1) is not operational in the cure context since \(B_i\) is not observed but it serves as our motivation for likelihood estimation and inference on \(\theta\) based on iid replicates \((Y_i, \Delta_i, X_i)\), \(1 \leq i \leq n\).

3.1 Likelihood estimation

We now define
\[
B_i^*(S_C) = B_i^*(Y_i, \Delta_i, X_i, S_C) = 1 - \frac{\Delta_i}{S_C(Y_i - | X_i)}, \tag{3.2}
\]
which, from (2.3), is such that \(\mathbb{E}\{B_i^*(S_C) \middle| X_i\} = \mathbb{E}(B_i \middle| X_i)\). Replacing \(B_i\) with \(B_i^*(S_C)\) in (3.1), we obtain the log-likelihood function which we propose in the case where \(S_C\) is known, that is
\[
\ell^*(\theta) = \sum_{i=1}^{n} [B_i^*(S_C) \log \pi_i(\theta) + \{1 - B_i^*(S_C)\} \log (1 - \pi_i(\theta))] \omega_i. \tag{3.3}
\]
Unlike (3.1), this likelihood is formed using the observable quantities \(Y_i\) and \(\Delta_i\) rather than the unobservable \(B_i\). Here, \(\omega_i = \omega(X_i)\) are positive weights. As will be explained in the sequel, the weight function \(\omega(X)\) is a technical device that will be needed when deriving general asymptotic results. However, we anticipate that in practically all applications \(\omega_i \equiv 1\). The score function, \(U^*(\theta) = \partial \ell^*(\theta) / \partial \theta = \sum_{i=1}^{n} U_i^*(\theta)\) where
\[
U_i^*(\theta) = \frac{B_i^*(S_C) - \pi_i(\theta)}{\pi_i(\theta)(1 - \pi_i(\theta))} \frac{\partial \pi_i(\theta)}{\partial \theta} \in \mathbb{R}^{p+1},
\]
is unbiased due to property (2.3); note that, in the case of a logistic cure regression model, we obtain the simplified expression \(U_i^*(\theta) = [B_i^*(S_C) - \pi_i(\theta)]X_i \omega_i\) with \(\pi_i(\theta) = \)
\frac{1}{1 + \exp(-\theta^\top X_i)}$. Furthermore, using standard inequalities, it can be shown that, when the cure regression model is identifiable,

\[ \mathbb{E}\{\ell^*(\theta)\} < \mathbb{E}\{\ell^*(\theta_0)\} \quad \forall \theta \neq \theta_0, \]  

where $\theta_0$ is the true parameter vector. See Lemma 8.3 in the Appendix. Hence, $\ell^*(\theta)$ is a legitimate criterion for estimation and inference on $\theta$.

Note that we have explicitly written $B^*_i(S_C)$ as a function of $S_C$ (while its dependence on $Y_i$, $\Delta_i$, and $X_i$ is implicit) since we must estimate $S_C$ in practice, i.e., we will use $B^*_i(\hat{S}_C)$. In applications of IPCW (recall that (2.3) is based on IPCW arguments), $S_C$ is typically estimated using a Kaplan-Meier or a Cox model, but one could also use more flexible non-parametric regression models such as those of Aalen (1980) or Beran (1981); in fact, the asymptotic theory of Section 4 only requires that the chosen estimator for $S_C$ has an iid representation. Thus, while our approach does not require specification or estimation of $S_{T_0}$, we must estimate $S_C$, and this can essentially be done in an arbitrarily flexible way. Therefore, for practical purposes, we propose the maximum likelihood estimator defined as

\[ \hat{\theta} = (\hat{\theta}(0), \hat{\theta}(1), \ldots, \hat{\theta}(p))^\top = \arg\max_{\theta} \ell^*(\theta) \quad (3.5) \]

where

\[ \ell^*(\theta) = \sum_{i=1}^{n} \left[ B^*_i(\hat{S}_C) \log \pi_i(\theta) + \{1 - B^*_i(\hat{S}_C)\} \log(1 - \pi_i(\theta)) \right] \omega_i. \quad (3.6) \]

The weights $\omega_i = \omega(X_i)$ will serve in theory to control the behavior of general estimates of $B^*_i(\hat{S}_C)$ in regions of low covariate density.

Of course, (3.6) is the familiar likelihood function used in logistic regression, (3.1), (hence, GLM estimation procedures can be used) but with $B_i$ replaced with $B^*_i = B^*_i(\hat{S}_C)$. The quantity $B^*$ plays a similar role to a “synthetic observation” as used by Koul et al. (1981) (see also Delecroix et al. (2008) and references therein) in least squares estimation for censored survival data. However, their response variable is a survival time, whereas we have a binary cure indicator. It is worth highlighting that current estimation procedures for semi-parametric cure models also involve replacing $B_i$ in (3.1) with an expected value, but in an iterative EM fashion (Peng and Dear, 2000; Sy and Taylor, 2000; Li and Taylor, 2002; Zhang and Peng, 2007), whereas $B^*_i(\hat{S}_C)$ is computed in one step followed by maximization of (3.6). The reason for this difference comes from the modeling approach. In the existing literature, models are assumed for both the conditional survival time of the uncured individuals, $S_{T_0}(t \mid X)$, and the cure proportion, $\pi(X)$, that together completely determine $S_T(t \mid X)$, while no assumptions are made about $S_C(t \mid X)$. Since $S_T(t \mid X)$ is directly identifiable from the observed data, the EM iterations between $S_{T_0}(t \mid X)$ and $\pi(X)$ represent a natural way to estimate these assumed model components. In contrast, our approach uses the fact that $S_C(t \mid X)$ can also be identified from the data, and, thus, we neither need to impose assumptions on $S_{T_0}(t \mid X)$ nor use an iterative procedure.
3.2 Penalized likelihood for variable selection

Selection of important variables has traditionally been carried out using best subset and stepwise procedures. However, these discrete approaches (variables are either in or out) are computationally intensive, their theoretical properties are not so well characterized (Fan and Li, 2001, 2002), coverage of confidence intervals for selected variables can be poor (Hurvich and Tsai, 1990; Zhang, 1992), and they are unstable in the sense that small changes to the data can result in large changes to the selected model and coefficients (Breiman, 1996). More modern approaches are based on penalized likelihood methods such as the least absolute shrinkage and selection operator (lasso) (Tibshirani, 1996), and these remove variables by estimating their coefficients as zero. Furthermore, the adaptive lasso (alasso) (Zou, 2006) enjoys the so-called oracle property (i.e., asymptotically, the estimates and standard errors are the same as if the true submodel was known and had simply been fitted without variable selection); the non-convex smoothly clipped absolute deviation (SCAD) penalty also possesses the oracle property (Fan and Li, 2001). Interestingly, the adaptive lasso is asymptotically related to (a continuous version of) best subset selection (Zhang and Lu, 2007).

The situation we consider for variable selection is the one where \( \pi(X; \theta) \) is a given function of \( X^\top \theta \) and thus \( X \in \mathbb{R}^{p+1} \) with \( X(0) \equiv 1 \). Then, by construction, the incorporation of a penalty term in our setup is straightforward, with the alasso estimator given by

\[
\hat{\theta}_\lambda = (\hat{\theta}_{\lambda,(0)}, \hat{\theta}_{\lambda,(1)}, \ldots, \hat{\theta}_{\lambda,(p)})^\top = \arg \max_{\theta \in \Theta} \hat{\ell}_\lambda^*(\theta)
\]

(3.7) where

\[
\hat{\ell}_\lambda^*(\theta) = \hat{\ell}^*(\theta) - \lambda \sum_{j=1}^p w_j |\theta(j)|
\]

(3.8)
is the penalized likelihood function, \( \hat{\ell}^*(\theta) \) is defined in (3.6), \( \lambda \geq 0 \) is the associated penalty parameter, and \( w_j \geq 0 \) are (potentially adaptive) weights, \( 1 \leq j \leq p \). Here, as is usual, the intercept, \( \theta(0) \), is not penalized in (3.7), and, furthermore, typically, the covariates will be standardized. Setting \( w_j = 1 \ \forall \ j \) yields the lasso penalty which penalizes all coefficients equally, while \( w_j = 1/|\hat{\theta}_{(j)}^{(0)}|^{\gamma} \) for some \( \gamma > 0 \) yields the alasso penalty (we will set \( \gamma = 1 \) as is most common in practice). In the latter case \( \hat{\theta}_{(j)}^{(0)} \) may be any consistent estimator of \( \theta_{(j)} \), and, typically, \( \hat{\theta}_{(j)}^{(0)} = \hat{\theta}_{(j)} \), where \( \hat{\theta}_{(j)} \) is the \( j \)th unpenalized estimator from (3.5). In Section 5.3 we provide details on implementation aspects of the alasso in our context.

4 Asymptotic results

Our asymptotic results are deduced under some minimal moment assumptions on the observed variables completed by some mild high-level assumptions on the cure regression model and on the model for the censoring variable. These conditions are quite natural in
the context of right-censored data when covariates are present and are to be verified on a case by case basis according to the context of the application. In this section we use the notation \( \pi(\theta) = \pi(X; \theta) \), \( \partial \pi(\theta) / \partial \theta = \partial \pi(X; \theta) / \partial \theta \), and \( B_i^*(S_C) \) (hence, \( B_i^*(\hat{S}_C) \)) as defined in equation (3.2).

**Assumption 4.1** (The data) The observations \((Y_i, \Delta_i, X_i), 1 \leq i \leq n, \) are independent replications of \((Y, \Delta, X) \in \mathbb{R} \times \{0, 1\} \times \mathcal{X}, \) where \( \mathcal{X} \) is some covariate space. Moreover, \( \mathbb{E}[\Delta/S_C(Y- | X)] < \infty. \)

Let \( \mathcal{M} = \{\pi(\theta) : \theta \in \Theta \subset \mathbb{R}^{p+1}\} \) be a generic parametric cure regression model, that is a set of functions of the covariate vector \( X \) indexed by \( \theta \) in some parameter space \( \Theta. \) For the logistic cure model, \( \pi(\theta) = 1/(1 + \exp(-\theta^\top X)). \)

### 4.1 Consistency

For the definition of a Glivenko-Cantelli class of function, we refer to the book by van der Vaart (2000).

**Assumption 4.2** (The cure regression model)

1. The weight \( \omega(X) \) is bounded, almost surely nonnegative and has a positive expectation.
2. There exists \( \theta_0 \in \Theta \) such that \( \Pr(T = \infty | X) = \pi(\theta_0). \) Moreover, there exists \( 0 < c < 1/2 \) such that, for any \( \theta \in \Theta, \) \( \Pr(c \leq \pi(\theta) \leq 1 - c) = 1. \)
3. For any \( \epsilon > 0, \) \( \inf_{\|\theta - \theta_0\| > \epsilon} \mathbb{E}[|\pi(\theta) - \pi(\theta_0)|\omega(X)] > 0. \)
4. The model \( \mathcal{M} \) is a \( \mathbb{P}_X \)-Glivenko-Cantelli class of functions of \( X \) with constant envelope.

**Assumption 4.3** (Uniform law of large numbers) The estimator \( \hat{S}_C(\cdot | \cdot) \) satisfies the law of large numbers uniformly over the class of the logit transformations of the functions in \( \mathcal{M}, \) that is

\[
\sup_{\theta \in \Theta} \left| \frac{1}{n} \sum_{i=1}^{n} \left[ B_i^*(\hat{S}_C) - B_i^*(S_C) \right] \omega(X_i) \log \left( \frac{\pi_i(\theta)}{1 - \pi_i(\theta)} \right) \right| = o_p(1).
\]

For simplicity, we consider a bounded weight \( \omega(X) \) and assume that the cure regressions in the model stay uniformly away from 0 and 1. The condition in Assumption 4.2-3 is a slightly reinforced identification condition that will guarantee that \( \theta_0 \) is a well-separated maximum of the expectation of the likelihood. It will be satisfied for instance in the logistic or probit regression as soon as the covariates are not redundant, that is whenever \( \mathbb{E}[XX^\top \omega(X)] \) is an invertible matrix.
Let us provide some mild sufficient conditions implying the uniform convergence of Assumption 4.3. These sufficient conditions involve a threshold that is commonly used in the literature of cure models. It is typically justified as representing a total follow-up of the study, and usually appears to have been considered independent of the covariates. However, we allow it to depend on the covariates in an arbitrary way.

Lemma 4.1 Assume that there exists \( \tau(x) \) such that, for any \( x \), \( \Pr(T_0 > \tau(x)) = 0 \) and \( \inf_{x \in X, \omega(x) > 0} S_C(\tau(x) - | x) > 0 \). Moreover, Assumptions 4.2-2 and 4.2-4 hold true. If

\[
\sup_{x \in X, \omega(x) > 0} \sup_{y \leq \tau(x)} \left| \hat{S}_C(y - | x) - S_C(y - | x) \right| = o_P(1),
\]

(4.1)

then the uniform convergence in Assumption 4.3 holds true.

The common parametric, semiparametric and nonparametric estimators \( \hat{S}_C \) satisfy condition (4.1). Several examples are provided in the monographs by Borgan et al. (1995) and Kalbfleisch and Prentice (2002), and, for convenience, some examples are recalled in the Appendix. The consistency of our maximum likelihood estimator is stated in the following results.

Proposition 4.2 If Assumptions 4.1, 4.2 and 4.3 hold true, then \( \hat{\theta} - \theta_0 = o_P(1) \).

Corollary 4.3 If Assumptions 4.1 and 4.2 hold true, and condition (4.1) is met, then \( \hat{\theta} - \theta_0 = o_P(1) \).

4.2 Asymptotic normality

Assumption 4.4 (The cure regression model)

1. For any \( x \in X \), the map \( \theta \mapsto \pi(x; \theta) \) is twice continuously differentiable.

2. The true value \( \theta_0 \) is an interior point of \( \Theta \),

\[
\mathbb{E} \left[ \left| \frac{\partial \pi(\theta_0)}{\partial \theta} \right|^2 \right] < \infty
\]

and the \( (p + 1) \times (p + 1) \)-matrix

\[
A(\theta_0) = \mathbb{E} \left[ \frac{\omega(X)}{\pi(\theta_0)[1 - \pi(\theta_0)]} \frac{\partial \pi(\theta_0)}{\partial \theta} \frac{\partial \pi(\theta_0)}{\partial \theta}^\top \right]
\]

is positive definite.
3. For any \(0 \leq k \leq l \leq p\), the families of functions of \(x\) indexed by \(\theta\)

\[
F_{1,kl} = \left\{ \frac{\partial^2 \pi}{\partial \theta(k) \partial \theta(l)}(x; \theta) : x \in X, \theta \in \Theta \right\}, \quad F_{2,kl} = \left\{ \left( \frac{\partial \pi}{\partial \theta(k)} \frac{\partial \pi}{\partial \theta(l)} \right)(x; \theta) : x \in X, \theta \in \Theta \right\}
\]

are \(\mathbb{P}_X\)–Glivenko-Cantelli classes of functions of \(X\) with integrable envelopes.

**Assumption 4.5** (I.I.D. representation) Let \(\varphi(X)\) be a vector-valued function such that \(\mathbb{E}\{\|\varphi(X)\|^2\} < \infty\). Then there exists \(\mu^C(Y, \Delta, X)\) a zero-mean vector-valued function that depends on \(\varphi(X)\), such that \(\mathbb{E}\{\|\mu^C(Y, \Delta, X)\|^2\} < \infty\) and

\[
\frac{1}{n} \sum_{1 \leq i \leq n} \left[ B^*_i(\hat{S}_C) - B^*_i(S_C) \right] \varphi(X_i) = \frac{1}{n} \sum_{1 \leq i \leq n} \mu^C(Y_i, \Delta_i, X_i) + o_P(n^{-1/2});
\]

Assumption 4.4 introduces mild standard regularity conditions on the cure regression model. In particular, Assumption 4.4-3 allows the uniform law of large numbers and guarantees that the remainder terms in the standard Taylor expansion used to prove asymptotic normality for MLE are uniformly negligible. Such an assumption on the complexity of the classes of first and second order derivatives of the functions in the model are satisfied by the standard parametric models such as logit and probit models. As an alternative to Assumption 4.4-3, we could impose condition (4.1) and slightly stronger regularity conditions on the model \(M\). The details are provided at the end of the proof of Proposition 4.4. A property as required in Assumption 4.5 is very common in survival analysis and is related to the so-called Kaplan-Meier integrals (cf. Stute (1996) and Gerds et al. (2017)). In the Appendix we provide several examples of models and estimators \(\hat{S}_C\) for which Assumption 4.5 holds true, namely Kaplan-Meier, conditional Kaplan-Meier, Cox proportional hazard, proportional odds and transformation models. In these examples, except for the case of the conditional Kaplan-Meier estimator, the weights \(\omega_i = \omega(X_i)\) will always be set equal to 1.

In general, the expression of the function \(\mu^C(Y, \Delta, X)\) in Assumption 4.5 depends on the joint law of the observations \((Y, \Delta, X)\). This function contributes to the asymptotic variance of our MLE \(\hat{\theta}\) that, hence, will be different from the asymptotic variance of the infeasible MLE defined with \(B^*(S_C)\) instead of \(B^*(\hat{S}_C)\).

**Proposition 4.4** Assume the conditions of Assumptions 4.1, 4.2 and Lemma 4.1 are met. Moreover, Assumption 4.4 holds true, and Assumption 4.5 is satisfied with

\[
\varphi(X) = \frac{\omega(X)}{\pi(\theta_0)[1 - \pi(\theta_0)]} \frac{\partial \pi(\theta_0)}{\partial \theta}.
\]

Then

\[
\hat{\theta} - \theta_0 = A(\theta_0)^{-1} \frac{1}{n} \sum_{i=1}^n \{ \mu(Y_i, \Delta_i, X_i; \theta_0) + \mu^C(Y_i, \Delta_i, X_i; \theta_0) \} + o_P(n^{-1/2}).
\]
where
\[
\mu(Y, \Delta, X; \theta_0) = \frac{[B^*(S_C) - \pi(\theta_0)] \omega(X)}{\pi(\theta_0)[1 - \pi(\theta_0)]} \frac{\partial \pi(\theta_0)}{\partial \theta}
\]
and \(\mu^C_c(Y, \delta, X)\) is the zero-mean vector-valued function from Assumption 4.3. In addition,
\[
\sqrt{n} \left( \hat{\theta} - \theta_0 \right) \rightsquigarrow N_{p+1} \left( 0, A(\theta_0)^{-1}V(\theta_0)A(\theta_0)^{-1} \right)
\]
with \(V(\theta_0) = \text{Var} \{ \mu(Y, \Delta, X; \theta_0) + \mu^C_c(Y, \Delta, X; \theta_0) \} \) (\(\rightsquigarrow\) denotes convergence in law.)

If suitable estimates of the vectors \(\mu(Y_i, \Delta_i, X_i; \theta)\) and \(\mu^C_c(Y_i, \Delta_i, X_i; \theta)\) are available, say, \(\hat{\mu}_i(\theta)\) and \(\hat{\mu}^C_c(\theta)\), then \(V(\theta_0)\) could be simply estimated by sample covariance,
\[
n^{-1} \sum_{i=1}^n \left[ \hat{\mu}_i(\hat{\theta}) + \hat{\mu}^C_c(\hat{\theta}) \right] \otimes \otimes 2 \\
\text{where } a \otimes = aa^T.
\]
Meanwhile, \(A(\theta_0)\) could also be estimated by standard methods, and thus one could derive an estimate of the variance of \(\hat{\theta}\). However, the estimates \(\hat{\mu}_i(\theta)\) and \(\hat{\mu}^C_c(\theta)\) are sometimes difficult to built. Alternatively, one can make use of the nonparametric bootstrap to approximate the law of \(\hat{\theta}\); indeed, we use this approach in our simulation studies and real data analysis.

### 4.3 Oracle properties for the adaptive lasso

In this section we prove consistency in variable selection for the adaptive lasso proposed in Section 3.2. Moreover, we prove the asymptotic normality for the true subset of coefficients. That is, we extend the Theorem 4 of [Zou, 2006] to the cure regression context. Let \(\theta_0 = (\theta_{0,(0)}, \theta_{0,(1)}, \ldots, \theta_{0,(p)})^\top\) be the true value of the cure regression parameter vector. Assume the true model has a sparse representation. Let \(A = \{ j : 1 \leq j \leq p, \theta_{0,(j)} \neq 0 \} \cup \{ 0 \}\). Without loss of generality, suppose \(A = \{ 0, 1, \ldots, p_0 \}\) with \(p_0 < p\). Below, the subscript \(A\) is used to define the subvectors or blocks in matrices with the components corresponding to the indices in the set \(A\). That is, \(\theta_{A,0}\) is the subvector of the first \(p_0 + 1\) components of \(\theta_0\), \(\partial \pi(\theta_0)/\partial \theta_A\) denotes the vector of \(p_0 + 1\) partial derivatives with respect to the first \(p_0 + 1\) components of \(\theta\), and \(A_A(\theta_0)\) is the upper-left block of dimension \((p_0 + 1) \times (p_0 + 1)\) of the \((p + 1) \times (p + 1)\) matrix \(A(\theta_0)\) defined in Assumption 4.4.2.

**Proposition 4.5** Assume the conditions of Proposition 4.4 are met and \(\pi(X; \theta)\) is a given function of \(X^\top \theta\). Let \(\hat{\theta}_\lambda\) be the estimator defined in equation (3.7) with \(w_j = 1/|\theta_{(j)}|^\gamma\) for some \(\gamma > 0\). Moreover, assume that \(\lambda/n \to 0\) and \(\lambda n^{(\gamma-1)/2} \to \infty\). Let \(A_n = \{ j : 1 \leq j \leq p, \hat{\theta}_{\lambda,(j)} \neq 0 \} \cup \{ 0 \}\). Then

1. \(\lim_{n \to \infty} \mathbb{P}(A_n = A) = 1\).
2. \(\hat{\theta}_{A,\lambda} - \theta_{A,0} = A_A(\theta_0)^{-1} \frac{1}{n} \sum_{i=1}^n \{ \mu_A(Y_i, \Delta_i, X_i; \theta_0) + \mu^C_A(Y_i, \Delta_i, X_i; \theta_0) \} + o_p(n^{-1/2})\)
where
\[ \mu_A(Y, \Delta, X; \theta_0) = \frac{[B^*(S_C) - \pi(\theta_0)] \omega(X)}{\pi(\theta_0)[1 - \pi(\theta_0)]} \frac{\partial \pi(\theta_0)}{\partial \theta_A} \]
and \( \mu_{A,C}(Y, \Delta, X; \theta_0) \) is the zero-mean vector-valued function from Assumption 4.3 considered with
\[ \varphi_A(X) = \frac{\omega(X)}{\pi(\theta_0)[1 - \pi(\theta_0)]} \frac{\partial \pi(\theta_0)}{\partial \theta_A}. \]

In addition,
\[ \sqrt{n} \left( \hat{\theta}_{A,\lambda} - \theta_{A,0} \right) \sim N_{p_0+1} \left( 0, A_A(\theta_0)^{-1} V_A(\theta_0) A_A(\theta_0)^{-1} \right) \]
with \( V_A(\theta_0) = \text{Var} \left\{ \mu_A(Y, \Delta, X; \theta_0) + \mu_{A,C}(Y, \Delta, X; \theta_0) \right\} \).

As was the case for Proposition 4.4, we can also obtain Proposition 4.5 by imposing condition (4.1) and slightly stronger regularity conditions on the model \( \mathcal{M} \) instead of Assumption 4.3.4.

5 Simulation studies

5.1 Setup
We first generate \( B, T_0 \) and \( C \), from which we obtain \( T = T_0 \) when \( B = 0 \) and \( T = \infty \) otherwise, and, hence, the observed time, \( Y = T \wedge C \), and censoring indicator, \( \Delta = (1 - B) \mathbb{1}(T_0 \leq C) \), respectively. The cure status is given by \( B \sim \text{Bernoulli}(\pi) \) where \( \pi(\theta) = 1/(1 + \exp(-X^T\theta)) \), \( X = (1, X_{(1)}, X_{(2)})^T \), and \( X_{(1)} \) and \( X_{(2)} \) are independent Normal(0, 1) variables. We set \( \theta_0 = (\theta_{0,0}, 1, 1)^T \) with \( \theta_{0,0} \in \{-1.85, -0.55\} \) such that the marginal cure proportion \( \pi_m = \mathbb{E}\{\pi(\theta)\} \in \{0.2, 0.4\} \). Consider the survivor function
\[ S_{T_0}(t \mid X) = \left\{ \frac{\exp(-t^\kappa) - \exp(-\tau^\kappa)}{1 - \exp(-\tau^\kappa)} \right\}^\psi \]
which is that of a truncated Weibull whose support is \((0, \tau)\) with a rate parameter, \( \psi \), and a shape parameter, \( \kappa \). The latency time, \( T_0 \), was generated according to this distribution with \( \psi = \exp(X^T\beta_{T_0}) \) and \( \kappa = (1/\psi)^\nu \) where \( \beta_{T_0} = (0, 0, 1)^T \) and \( \nu \in \{0, 2\} \); the proportional hazards property holds when \( \nu = 0 \). The value of \( \tau \) was set at the 95th percentile of the marginal untruncated distribution, i.e., \( \tau \) is the unique solution of the equation
\[ \mathbb{E}\left\{ \exp(-\tau^\kappa) \right\}^\psi = 0.05. \]
Clearly, \( \tau \) depends on the value of \( \nu \). Lastly, the censoring time, \( C \), was generated from an exponential distribution with rate parameter \( \psi_C = \exp(X^T\beta_C) \) where \( \beta_C = (\beta_{C,(0)}, 0, 1)^T \). The value \( \beta_{C,(0)} \) was chosen such that the overall censored proportion is given by \( \pi_{cen} = \Pr(\Delta = 0) = \pi_m + \rho \) where \( \rho \in \{0.1, 0.2\} \), and this depends on the values
of θ(0) and ν; since πm ∈ {0.2, 0.4}, there are then four values for the censoring proportion, πcen ∈ {0.3, 0.4, 0.5, 0.6}.

It is worth highlighting that X(1) only affects cure probability (since βT0,(1) = βC,(1) = 0), whereas X(2) affects all components of the data generating process (since θ(2) = βT0,(2) = βC,(2) = 1). Sample sizes of n ∈ {100, 300, 1000} were considered, and, with two values for each of θ(0), ν, and ρ, there are 24 scenarios altogether. Each simulation scenario was replicated 2000 times.

5.2 Estimation procedure

We applied the estimation scheme described in Section 3 to the simulated data with SC estimated using a Cox model in which both covariates, X(1) and X(2), appear as predictors. Table 1 displays the average bias and standard error of estimates over simulation replicates. While the bias can be somewhat large when n = 100, this vanishes as the sample size increases. Similarly, the standard errors also decrease with the sample size. As we might expect, the estimates generally disimprove when the censoring proportion increases. Furthermore, the results do not change appreciably when ν is varied (i.e., the approach is not sensitive to the form of ST0), while the standard errors decrease a little when πm is increased. Table 2 shows the empirical coverage for 95% confidence intervals constructed using bootstrapping with 399 replicates; we find that the empirical coverage is close to the nominal level.

By way of comparison, we also applied the EM approach of Peng and Dear (2000) and Sy and Taylor (2000) which has been implemented in the smcure (Chao et al., 2012) package in R (R Core Team, 2018). In contrast to our scheme, ST0 must be estimated rather than SC. Thus, ST0 was estimated using a Cox model in which both covariates, X(1) and X(2), appear as predictors. The results, shown in Table 3, are broadly similar to those in Table 1 albeit the smcure estimates are generally more efficient. This was expected since the smcure estimates take into account the model imposed to ST0, while our assumption is fully nonparametric in that respect. An important difference is the fact that, when ST0 does not have the proportional hazards property (i.e., when ν = 2), we see bias in the smcure estimates which does not disappear with increasing sample size. In particular, the bias manifests through θ(0) and θ(2); interestingly, θ(1) is unaffected (i.e., the coefficient of X(1), the covariate which only enters the cure component).

5.3 Selection procedure

A variety of algorithms have been implemented for solving non-differentiable lasso problems, e.g., quadratic programming (Tibshirani, 1996), least angle regression (LARS) (Efron et al., 2004), and co-ordinate descent (Friedman et al., 2007). However, we prefer the use of a differentiable penalty since standard gradient-based optimization procedures
Table 1: Average bias and standard error (in brackets) of estimates

| $\nu$ | $\pi_m$ | $\rho$ | $\theta_0$ | $\theta_1$ | $\theta_2$ | $\theta_0$ | $\theta_1$ | $\theta_2$ | $\theta_0$ | $\theta_1$ | $\theta_2$ |
|-------|---------|--------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| 0     | 0.2     | 0.1    | -0.20       | 0.14        | 0.12        | -0.06       | 0.05        | 0.03        | -0.01       | 0.01        | 0.01        |
|       |         |        | (0.65)      | (0.62)      | (0.58)      | (0.29)      | (0.29)      | (0.26)      | (0.15)      | (0.14)      | (0.14)      |
| 0.2   | 0.2     | 0.12   | -0.17       | 0.12        | 0.12        | -0.06       | 0.05        | 0.05        | -0.02       | 0.01        | 0.02        |
|       |         |        | (0.80)      | (0.74)      | (0.68)      | (0.40)      | (0.40)      | (0.34)      | (0.20)      | (0.20)      | (0.17)      |
| 0.4   | 0.1     | 0.10   | -0.05       | 0.10        | 0.12        | -0.01       | 0.04        | 0.03        | 0.00        | 0.01        | 0.01        |
|       |         |        | (0.36)      | (0.49)      | (0.47)      | (0.18)      | (0.24)      | (0.22)      | (0.10)      | (0.12)      | (0.12)      |
| 0.2   | 0.2     | 0.16   | -0.03       | 0.16        | 0.17        | -0.02       | 0.05        | 0.05        | 0.00        | 0.02        | 0.02        |
|       |         |        | (0.51)      | (0.74)      | (0.66)      | (0.29)      | (0.37)      | (0.32)      | (0.13)      | (0.18)      | (0.16)      |
| 2     | 0.2     | 0.12   | -0.16       | 0.12        | 0.11        | -0.05       | 0.04        | 0.03        | -0.01       | 0.01        | 0.01        |
|       |         |        | (0.62)      | (0.60)      | (0.51)      | (0.29)      | (0.29)      | (0.24)      | (0.15)      | (0.15)      | (0.13)      |
| 0.2   | 0.2     | 0.13   | -0.13       | 0.13        | 0.10        | -0.09       | 0.07        | 0.06        | -0.02       | 0.01        | 0.01        |
|       |         |        | (0.80)      | (0.76)      | (0.60)      | (0.45)      | (0.43)      | (0.32)      | (0.21)      | (0.20)      | (0.15)      |
| 0.4   | 0.1     | 0.13   | -0.05       | 0.13        | 0.11        | -0.02       | 0.04        | 0.02        | 0.00        | 0.01        | 0.01        |
|       |         |        | (0.37)      | (0.53)      | (0.44)      | (0.19)      | (0.25)      | (0.21)      | (0.10)      | (0.13)      | (0.11)      |
| 0.2   | 0.2     | 0.15   | -0.03       | 0.15        | 0.15        | -0.02       | 0.06        | 0.05        | -0.01       | 0.02        | 0.01        |
|       |         |        | (0.55)      | (0.77)      | (0.60)      | (0.30)      | (0.41)      | (0.27)      | (0.15)      | (0.20)      | (0.13)      |
Table 2: Empirical coverage of 95% bootstrapped confidence intervals

| $\nu$ | $\pi_m$ | $\rho$ | $\theta_{(0)}$ | $\theta_{(1)}$ | $\theta_{(2)}$ | $n = 100$ | $n = 300$ | $n = 1000$ |
|-------|--------|--------|----------------|----------------|---------------|------------|------------|------------|
| 0     | 0.2    | 0.1    | 91.2 93.2 93.9 | 93.5 93.2 94.3 | 94.0 94.8 94.0 |
|       |        |        | 94.7 95.0 94.8 | 94.8 94.5 93.2 | 93.8 93.0 93.5 |
| 0.2   |        |        | 94.6 93.6 93.4 | 94.8 94.0 94.9 | 94.7 94.4 94.8 |
|       |        |        | 94.7 94.2 93.8 | 93.9 94.4 93.8 | 94.7 94.0 94.2 |
| 0.4   | 0.1    |        | 92.9 94.3 93.4 | 93.9 93.5 94.8 | 94.2 94.3 94.9 |
|       |        |        | 95.9 95.3 96.1 | 94.5 94.9 94.1 | 93.0 95.0 95.3 |
| 0.2   |        |        | 93.3 93.0 92.4 | 93.9 94.6 94.6 | 95.0 93.8 95.0 |
|       |        |        | 94.7 95.3 94.1 | 94.0 94.4 95.3 | 94.2 94.5 94.9 |
| 2     | 0.2    | 0.1    | 90.8 93.6 93.3 | 93.2 93.5 93.9 | 94.0 93.8 93.2 |
|       |        |        | 94.8 96.1 95.5 | 94.6 94.1 94.0 | 94.5 94.2 94.0 |
| 0.2   |        |        | 94.1 93.2 92.6 | 94.2 92.6 93.2 | 94.6 94.0 94.3 |
|       |        |        | 96.0 95.8 95.0 | 94.2 94.3 94.4 | 94.4 94.0 94.0 |
| 0.4   | 0.1    |        | 92.1 94.4 93.8 | 93.2 93.6 93.5 | 93.5 93.3 93.8 |
|       |        |        | 94.5 95.3 95.8 | 93.5 95.2 93.3 | 94.0 94.0 93.8 |
| 0.2   |        |        | 94.5 94.0 94.0 | 94.2 92.9 93.2 | 94.0 94.5 94.1 |
|       |        |        | 95.0 94.8 94.6 | 94.9 94.7 95.5 | 93.6 93.5 94.1 |
Table 3: Average bias and standard error (in brackets) of smcure estimates

| $\nu$ | $\pi_m$ | $\rho$ | $\theta_{(0)}$ | $\theta_{(1)}$ | $\theta_{(2)}$ | $\theta_{(0)}$ | $\theta_{(1)}$ | $\theta_{(2)}$ | $\theta_{(0)}$ | $\theta_{(1)}$ | $\theta_{(2)}$ |
|-------|--------|-------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|---------------|
| 0     | 0.2    | 0.1   | -0.20         | 0.12          | 0.08          | -0.05         | 0.04          | 0.02          | -0.02         | 0.01          | 0.01          |
|       |        |       | (0.54)        | (0.48)        | (0.46)        | (0.25)        | (0.23)        | (0.22)        | (0.14)        | (0.12)        | (0.12)        |
| 0.2   |        |       | -0.40         | 0.20          | 0.14          | -0.09         | 0.04          | 0.05          | -0.03         | 0.02          | 0.02          |
|       |        |       | (0.93)        | (0.72)        | (0.68)        | (0.34)        | (0.30)        | (0.27)        | (0.17)        | (0.15)        | (0.14)        |
| 0.4   | 0.1    |       | -0.08         | 0.09          | 0.09          | -0.02         | 0.03          | 0.02          | -0.01         | 0.01          | 0.01          |
|       |        |       | (0.33)        | (0.40)        | (0.38)        | (0.17)        | (0.20)        | (0.19)        | (0.09)        | (0.11)        | (0.10)        |
| 0.2   |        |       | -0.25         | 0.20          | 0.12          | -0.06         | 0.05          | 0.03          | -0.01         | 0.02          | 0.01          |
|       |        |       | (0.64)        | (0.68)        | (0.61)        | (0.26)        | (0.27)        | (0.25)        | (0.12)        | (0.14)        | (0.13)        |
| 2     | 0.2    | 0.1   | -0.16         | 0.11          | -0.03         | -0.03         | 0.02          | -0.07         | 0.00          | 0.00          | -0.09         |
|       |        |       | (0.54)        | (0.48)        | (0.42)        | (0.25)        | (0.23)        | (0.20)        | (0.13)        | (0.12)        | (0.11)        |
| 0.2   |        |       | -0.18         | 0.12          | -0.10         | -0.02         | 0.02          | -0.14         | 0.04          | -0.02         | -0.16         |
|       |        |       | (0.73)        | (0.59)        | (0.48)        | (0.33)        | (0.27)        | (0.23)        | (0.17)        | (0.14)        | (0.11)        |
| 0.4   | 0.1    |       | -0.12         | 0.10          | -0.09         | -0.08         | 0.04          | -0.13         | -0.06         | 0.01          | -0.13         |
|       |        |       | (0.35)        | (0.40)        | (0.33)        | (0.19)        | (0.21)        | (0.17)        | (0.10)        | (0.11)        | (0.09)        |
| 0.2   |        |       | -0.22         | 0.15          | -0.17         | -0.12         | 0.05          | -0.20         | -0.09         | 0.01          | -0.20         |
|       |        |       | (0.55)        | (0.57)        | (0.42)        | (0.28)        | (0.27)        | (0.20)        | (0.14)        | (0.13)        | (0.10)        |
can then be utilized. Therefore, we propose the use of

\[ \hat{l}_{\lambda, \epsilon}(\theta) = \hat{l}(\theta) - \lambda \sum_{j=1}^{p} w_j a_\epsilon(\theta_{(j)}) \]  

(5.1)

where \( a_\epsilon(x) = (x^2 + \epsilon^2)^{1/2} - \epsilon \) is an extension of the absolute value function such that \( \lim_{\epsilon \to 0} a_\epsilon(x) = |x| \), and which is differentiable for \( \epsilon > 0 \). Clearly, smaller \( \epsilon \) values bring the penalty closer to the lasso, but also bring (5.1) closer to being non-differentiable. In our work, we have found that \( \epsilon = 10^{-4} \) works well.

For the purpose of selecting the tuning parameter, \( \lambda \), we consider cross-validation; in particular we aim to minimize the \( k \)-fold cross-validation error. First, since \( E\{B_1^n|SC) - \pi_i(\theta) | X_i\} = 0 \), we may define the error term, \( B_1^n(\hat{SC}) - \pi_i(\hat{\theta}_1) \). Then, for a partition \( F_1, \ldots, F_K \) of the set \( \{1, \ldots, n\} \), the mean-squared error for the \( j \)th fold, \( F_j \) is given by \( \sum_{i \in F_j} (B_1^n(\hat{SC}) - \pi_i(\hat{\theta}_1))^2 \) where \( \hat{\theta}_1 \) is the penalized estimate with the \( j \)th fold removed. Thus, the \( k \)-fold cross-validation error is given by

\[ \text{CVE}(\lambda) = \frac{1}{k} \sum_{j=1}^{k} \sum_{i \in F_j} \left( B_1^n(\hat{SC}) - \pi_i(\hat{\theta}_1) \right)^2 \]  

(5.2)

where we will use \( k = 10 \) as is standard in practice. Minimizing (5.2) with respect to \( \lambda \) can be achieved by profiling over a range of \( \lambda \) values or by using a one-dimensional optimizer, e.g., golden search; we will define \( \lambda_{\text{CVE}} \) to be the minimizer of (5.2).

In order to test our proposed selection procedure, we simulated data as described in Section 5.1, but with four additional independent Normal(0,1) variables, namely, \( X_{(3)} \), \( X_{(4)} \), \( X_{(5)} \), and \( X_{(6)} \). These variables do not affect probability of cure, i.e., their \( \theta \) coefficients are zero, but we set \( \beta_{T_0,(3)} = \beta_{C,(3)} = 1 \) so that \( X_{(3)} \) affects other aspects of the data generating process; the \( \beta_{T_0} \) and \( \beta_C \) coefficients for \( X_{(4)}, X_{(5)} \), and \( X_{(6)} \) are all zero. We then define the following metrics to assess the variable selection procedure:

\[ C = \sum_{j=4}^{6} 1(\hat{\theta}_{\lambda_{\text{CVE}},(j)} = 0), \]

\[ \text{IC} = \sum_{j=1}^{2} 1(\hat{\theta}_{\lambda_{\text{CVE}},(j)} = 0), \]

\[ \text{DF} = \sum_{j=0}^{6} 1(\hat{\theta}_{\lambda_{\text{CVE}},(j)} > 0), \]

where \( C \) is the number of coefficients correctly set to zero, \( \text{IC} \) is the number of coefficients incorrectly set to zero, and \( \text{DF} \) is the model degrees of freedom (i.e., the number of non-zero parameters); in our setup, for the oracle model, \( C = 4 \), \( \text{IC} = 0 \), and \( \text{DF} = 3 \). These metrics, averaged over simulation replicates, are shown in Table 4.
| Type | $\nu$ | $\pi_m$ | $\rho$ | $n = 100$ | $n = 300$ | $n = 1000$ |
|------|------|-------|------|--------|--------|--------|
|      |      |       |      | C | IC | DF | C | IC | DF | C | IC | DF |
| oracle |      |       |      | 4.00 | 0.00 | 3.00 | 4.00 | 0.00 | 3.00 | 4.00 | 0.00 | 3.00 |
| lasso | 0    | 0.2   | 0.1  | 2.86 | 0.37 | 3.77 | 2.39 | 0.00 | 4.61 | 2.31 | 0.00 | 4.69 |
|       | 0.2  | 3.23  | 0.79 | 2.98 | 2.66 | 0.06 | 4.29 | 2.54 | 0.00 | 4.46 |
|       | 0.4  | 2.52  | 0.11 | 4.37 | 2.33 | 0.00 | 4.67 | 2.30 | 0.00 | 4.70 |
|       | 0.2  | 2.90  | 0.45 | 3.65 | 2.51 | 0.02 | 4.47 | 2.44 | 0.00 | 4.56 |
|       | 2    | 0.2   | 0.1  | 2.76 | 0.34 | 3.90 | 2.40 | 0.00 | 4.60 | 2.28 | 0.00 | 4.72 |
|       | 0.2  | 3.19  | 0.85 | 2.96 | 2.64 | 0.09 | 4.27 | 2.46 | 0.00 | 4.53 |
|       | 0.4  | 2.58  | 0.10 | 4.32 | 2.37 | 0.00 | 4.63 | 2.24 | 0.00 | 4.76 |
|       | 0.2  | 2.92  | 0.48 | 3.60 | 2.50 | 0.05 | 4.45 | 2.43 | 0.00 | 4.57 |
| alasso | 0    | 0.2   | 0.1  | 3.44 | 0.37 | 3.19 | 3.47 | 0.01 | 3.52 | 3.67 | 0.00 | 3.33 |
|       | 0.2  | 3.50  | 0.74 | 2.76 | 3.50 | 0.09 | 3.41 | 3.69 | 0.00 | 3.31 |
|       | 0.4  | 3.34  | 0.17 | 3.49 | 3.52 | 0.00 | 3.48 | 3.69 | 0.00 | 3.31 |
|       | 0.2  | 3.40  | 0.47 | 3.13 | 3.45 | 0.05 | 3.50 | 3.67 | 0.00 | 3.32 |
|       | 2    | 0.2   | 0.1  | 3.35 | 0.36 | 3.30 | 3.48 | 0.01 | 3.51 | 3.65 | 0.00 | 3.35 |
|       | 0.2  | 3.47  | 0.77 | 2.76 | 3.46 | 0.13 | 3.42 | 3.65 | 0.00 | 3.35 |
|       | 0.4  | 3.33  | 0.15 | 3.52 | 3.55 | 0.00 | 3.44 | 3.72 | 0.00 | 3.28 |
|       | 0.2  | 3.38  | 0.47 | 3.15 | 3.42 | 0.07 | 3.50 | 3.64 | 0.01 | 3.35 |
The IC values tend towards zero as the sample size increases for both the lasso and alasso. However, the lasso tends to select a more complex model than the alasso as indicated by the smaller C values and larger DF values; it is well known that the lasso exhibits this behaviour (Fan and Lv, 2010). Overall, the alasso appears to work well with C approaching the oracle value of four as the sample size increases. The results are unaffected by the value of \( \nu \) as we might expect, whereas, when \( n = 100 \), increased censoring proportion, \( \rho \), or decreased cure proportion, \( \pi_m \), both lead to fewer variables being selected.

6 Data analysis

6.1 Overview of data

We consider two datasets for the purpose of analysis, namely (i) the well known colon cancer dataset (Moertel et al., 1990) contained in the survival package in R and (ii) a melanoma dataset (Kirkwood et al., 1996) contained in the smcure package in R. Both were randomized controlled trials which evaluated adjuvant chemotherapy following surgery where relapse-free survival was considered, i.e., time from randomization until the earlier of cancer relapse or death. These datasets are candidates for cure analysis based on their Kaplan-Meier (KM) curves (Figure 1) which level off over time — approximately at 40% for the colon cancer data and 30% for the melanoma data. Indeed the last value in the KM curve is a valid estimator of the marginal cure probability (Maller and Zhou, 1992) and our approach reduces to this when there are no covariates (i.e., \( X \equiv 1 \)); see Satten and Datta (2001) for details.

The colon and melanoma datasets are described in more detail and analysed in Sections 6.2 and 6.3 below respectively. In particular, we estimate the cure parameters using our proposed likelihood procedure (see Section 3) and, for comparison, we apply smcure with signs of the coefficients reversed (to align with our model for the cure probability, rather than the non-cure probability). We use a Cox model with all covariates for the estimation of \( S_C \) in our approach and the estimation of \( S_{T_0} \) in smcure, and confidence intervals and p-values are produced using bootstrapping in both cases. We also carry out variable selection using lasso and adaptive lasso (see Sections 3.2 and 5.3); covariates are standardized for the purpose of selection, after which the cure estimates are transformed back to correspond to the original scale.

6.2 Colon cancer data

This was a national intergroup study (involving Eastern Cooperative Oncology Group, the North Central Cancer Treatment Group, the Southwest Oncology Group, and the Mayo Clinic) to investigate the efficacy of the drugs levamisole and 5FU (fluorouracil) for the treatment of colon cancer following surgery. In total, 929 patients with stage C disease were enrolled during the period March 1984 to October 1987, with a maximum follow-
up time of approximately nine years. These patients were randomized to the following
treatments: observation (control / reference group), levamisole, and a combined treatment
of levamisole and 5FU. In addition to the treatment variable, a variety of binary covariates
were recorded (reference categories are shown first): days since surgery, \{≤ 20, > 20\}; sex,
\{female, male\}; obstruction of colon by tumour, \{no, yes\}; adherence to nearby organs,
\{no, yes\}; depth of invasion, \{submucosa or muscular layer, serosa\}; positive lymph nodes,
\{≤ 4, > 4\}. Furthermore, the age of the patient was also recorded, and we use a mean-
centered version (the mean age is 59.75 years). See Moertel et al. (1990) for further
details.

Table 5: Colon cancer estimates

| Covariate      | Unpenalized |             |       | Penalized |             |       | ssmcure |
|----------------|-------------|-------------|-------|-----------|-------------|-------|---------|
|                | Est.        | 95%CI       | pval  | Est.      | 95%CI       | pval  |         |
| Intercept      | 0.66        | (0.05, 1.36)| 0.03  | 0.66      | 0.32         | 0.03  | 0.57    |
| Treatment      | Lev         | (0.11, 1.22)| 0.14  | 0.42      | 0.00         | 0.19  | (-0.21, 0.61) | 0.33 |
|                | Lev+5FU     | 0.39        | 0.73  | 0.42      | 0.00         | 0.19  | (-0.21, 0.61) | 0.33 |
| Surgery        | > 20days    | -1.63       | -0.11 | -0.65     | -0.41        | -0.49 | (-0.88, -0.09) | 0.01 |
| Age (centered) | Years       | -0.03       | 0.00  | -0.01     | 0.00         | -0.01 | (-0.02, 0.00) | 0.24 |
| Sex            | Male        | -0.75       | 0.16  | -0.24     | 0.00         | -0.24 | (-0.46, 0.25) | 0.60 |
| Obstruction    | Yes         | -2.01       | 0.05  | -0.56     | -0.19        | -0.56 | (-0.61, 0.20) | 0.35 |
| Adherence      | Yes         | -1.00       | 0.07  | -0.42     | 0.00         | -0.42 | (-1.50, -0.17) | 0.01 |
| Depth          | Serosa      | -1.51       | 0.26  | -0.81     | -0.54        | -0.81 | (-1.27, -0.19) | 0.02 |
| Nodes          | > 4         | -1.63       | 0.82  | -1.18     | -0.94        | -1.16 | (-1.59, -0.80) | 0.00 |

The estimated cure parameters are shown in Table 5. We first consider the results for
Figure 2: Adaptive lasso regularization paths for colon data. Coefficient estimates, denoted by \( \hat{\theta} \), are for the standardized covariates (hence, their magnitudes can be directly compared), and these are plotted against the tuning parameter \( \lambda = \lambda/n \). Also shown is the 10-fold cross-validation error curve (see right-hand y-axis) with a vertical line indicating the minimum error point.
our unpenalized approach. The effect of the levamisole treatment does not significantly increase the cure probability (compared with a patient receiving no treatment), while the combination of levamisole with 5FU does; indeed, the odds of being cured for this latter treatment are 2.56 (= exp(0.94)) with 95% confidence interval given by (1.48, 5.64). The effect of all other covariates is to reduce the cure probability, albeit sex is not statistically significant, and obstruction and adherence are only just significant at the 10% level. The results for smcure are broadly similar, apart from the fact that adherence is statistically significant.

In this particular application, the lasso has not performed any shrinkage of coefficients (i.e., the optimal λ value selected was zero) which is in line with the typical behaviour of lasso to over-select covariates. On the other hand, the adaptive lasso has set several coefficients to zero, and the retained variables are those with smaller p-values from the unpenalized model. The regularization paths for standardized cure coefficients (i.e., those corresponding to standardized covariates) provide useful information on the relative importance of each covariate; these are shown for adaptive lasso in Figure 2. We can see immediately that the Lev+5FU treatment is one of the most important features. The number of positive lymph nodes is also highly important, and the presence of more than four such lymph nodes reduces the chance of cure. Next, the timing of surgery and depth of the tumour have similar importance, followed by the presence of an obstruction.

### 6.3 Melanoma data

The Eastern Cooperative Oncology Group (ECOG) trial EST 1684 recruited patients (284 altogether) between 1984 and 1990, with the study ending in 1993. The aim of this study was to evaluate interferon alfa-2b (IFNo-2b) as an adjuvant therapy for melanoma following surgery. Thus, patients were randomly assigned to one of two arms: observation (control / reference group), and treatment with IFNo-2b. Furthermore, the age and sex of the patient was recorded (and we mean-center age where the mean is 47.03 years). See Kirkwood et al. (1996) for further details.

Following Section 6.2, we present the unpenalized and penalized estimates along with the estimates from smcure in Table 6. Treatment is highly statistically significant (p-value < 0.01), while age comes in just under the 5% level of significance; sex is not statistically significant. The results from smcure are qualitatively similar, although age is not statistically significant. Both the lasso and adaptive lasso penalties remove sex from the model. The standardized regularization path for the adaptive lasso (Figure 3) confirms that treatment is the variable which impacts the probability of cure the most, having a curative effect, while age reduces the cure probability (albeit the magnitude of this effect is lower than that of treatment).
Table 6: Melanoma estimates

| Covariate       | Unpenalized | Penalized | Penalized smcure |
|-----------------|-------------|-----------|------------------|
|                 | Est.        | 95%CI     | pval             | Est.        | 95%CI     | pval             | Est.        | 95%CI     | pval             |
| Intercept       | -1.40       | (-2.96,-0.79) | 0.00        | -1.29       | -1.40     |               | -1.28       | (-2.10,-0.70) | 0.00             |
| Treatment IFN   | 1.01        | (0.25, 2.96)  | 0.00        | 0.54        | 0.72      |               | 0.59        | (-0.02, 1.37)  | 0.05             |
| Age (centered) Years | -0.03       | (-0.08, 0.00) | 0.04        | -0.01       | -0.01     |               | -0.02       | (-0.05, 0.01)  | 0.13             |
| Sex Male        | -0.33       | (-1.57, 0.40) | 0.43        | 0.00        | 0.00      |               | -0.09       | (-0.73, 0.52)  | 0.79             |

Figure 3: Adaptive lasso regularization path for melanoma data. Coefficient estimates, denoted by $\tilde{\theta}$, are for the standardized covariates (hence, their magnitudes can be directly compared), and these are plotted against the tuning parameter $\tilde{\lambda} = \lambda/n$. Also shown is the 10-fold cross-validation error curve (see right-hand $y$-axis) with a vertical line indicating the minimum error point.
7 Discussion

We have proposed an IPCW-based likelihood estimation procedure for cure regression models; elsewhere IPCW has been advocated by Gerds et al. (2017) as a device for producing straightforward estimators in complex survival data. In contrast to current cure estimation procedures in the literature, our assumptions are placed on $S_C$ while $S_{T_0}$ is unspecified. Although we have considered a Cox model estimator for $S_C$ in the examples in this article, any arbitrarily flexible model can be used in practice as this simply “plugs in” to the likelihood function given in (3.6) – or the penalized likelihood given in (3.8) – without any added complexity to the estimation procedure; indeed, it is a (penalized) GLM procedure. Moreover, our asymptotic results still hold once the estimator, $\hat{S}_C$, permits an iid representation (and we have given many common examples in the Appendix).

Except for the case of a fully nonparametric approach like in Xu and Peng (2014) (which suffers from the curse of dimensionality), the existing cure regression models have to impose assumptions on both the cure proportion and the law of the susceptible individuals, without the possibility for model diagnosis (besides ad-hoc efforts). In our approach, one can first use standard diagnosis procedures to validate the censoring law model as this is identifiable from the observed data directly. For example, one could assess the proportional hazards assumption for $S_C$ using the test due to Grambsch and Therneau (1994) which is implemented in the `cox.zph` function in the `survival` package in R. (Although not shown, this test supported the proportional hazards assumption in the applications considered in Section 6.) Next one could consider model diagnostics for the cure regression, e.g., based on error terms of the form $B_i^*(\hat{S}_C) - \pi_i(\hat{\theta})$ which we made use of in (5.2). Furthermore, note that our theory is not limited to the logistic model choice used in our applications, and, more generally still, the functional form of the cure regression model $\pi(X^T\theta)$ could itself be estimated. Goodness-of-fit for the cure model and estimation of its functional form are beyond the scope of the current article but will be developed in our future work.
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8 Appendix

8.1 Proofs

Lemma 8.1 Let $B$ be a Bernoulli random variable, $T_0$ a nonnegative random variable and let $T = T_0$ if $B = 0$ and $T = \infty$ if $B = 1$. Then

$$T_0 \perp C \mid X \text{ and } B \perp (T_0, C) \mid X \implies T \perp C \mid X.$$ 

Proof of Lemma 8.1. By elementary properties of conditional independence

$$B \perp (T_0, C) \mid X \iff B \perp C \mid (X, T_0) \text{ and } B \perp T_0 \mid X.$$ 

Next,

$$B \perp C \mid (X, T_0) \text{ and } T_0 \perp C \mid X \iff (B, T_0) \perp C \mid X.$$ 

The result follows from the fact that $T$ is completely determined by $B$ and $T_0$.

Lemma 8.2 Let $r(Y, X)$ be an integrable real-valued function. Under conditions (2.1) and (2.2), we have

$$\mathbb{E}\left( \frac{\Delta r(Y, X)}{S_C(Y \mid X)} \mid X \right) = \mathbb{E}\{r(T_0, X) \mid X\} \{1 - \pi(X)\}.$$ 

Proof of Lemma 8.2. First, we have that

$$\mathbb{E}\left( \frac{\Delta r(Y, X)}{S_C(Y \mid X)} \mid X \right) = \mathbb{E}\left( \frac{\Delta r(T_0, X)}{S_C(T_0 \mid X)} \mid X \right)$$

since only the $\Delta = 1$ case contributes where $Y = T_0$. Next,

$$\mathbb{E}(\Delta \mid T_0, X) = \mathbb{E}\{1(T_0 \leq C)(1 - B) \mid T_0, X\}$$

$$= \mathbb{E}\{1(T_0 \leq C)\mathbb{E}(1 - B \mid C, T_0, X) \mid T_0, X\}$$

$$= \mathbb{E}\{1(T_0 \leq C) \mid T_0, X\} \mathbb{E}(1 - B \mid X)$$

$$= S_C(T_0 - \mid X) \mathbb{E}(1 - B \mid X),$$

where $\mathbb{E}(1 - B \mid C, T_0, X) = \mathbb{E}(1 - B \mid X)$ follows from (2.2), and $\mathbb{E}[1(T_0 \leq C) \mid T_0, X] = S_C(T_0 - \mid X)$ follows from (2.1). Bringing the above together, we then have

$$\mathbb{E}\left( \frac{\Delta r(Y, X)}{S_C(Y \mid X)} \mid X \right) = \mathbb{E}\left( \frac{\Delta r(T_0, X)}{S_C(T_0 \mid X)} \mid X \right)$$

$$= \mathbb{E}\left\{ \frac{r(T_0, X)}{S_C(T_0 \mid X)} \mathbb{E}(\Delta \mid T_0, X) \mid X \right\}$$

$$= \mathbb{E}\{r(T_0, X)\mathbb{E}(1 - B \mid X) \mid X\}$$

$$= \mathbb{E}\{r(T_0, X) \mid X\} \{1 - \pi(X)\},$$

as required.
Lemma 8.3 Let
\[ \ell^*(\theta) = \sum_{i=1}^{n} [B_i^*(S_C) \log \pi_i + \{1 - B_i^*(S_C)\} \log(1 - \pi_i)] \omega_i. \]

If the cure regression model is identifiable,
\[ \mathbb{E}\{\ell^*(\theta)\} < \mathbb{E}\{\ell^*(\theta_0)\} \quad \forall \theta \neq \theta_0 \]

Proof of Lemma 8.3. Let \( \pi^*(X) = \mathbb{E}\{B_i^*(S_C) \mid X\} \), which by construction lies between 0 and 1. Then, since for any \( u > 0, \log(u) \leq u - 1 \), we deduce
\[
\mathbb{E}\{\ell^*(\theta)\} - \mathbb{E}\{\ell^*(\theta_0)\} = \mathbb{E}\{\mathbb{E}\{\ell^*(\theta)\} \mid X\} - \mathbb{E}\{\mathbb{E}\{\ell^*(\theta_0)\} \mid X\}
\]
\[
= \mathbb{E}\left\{ \pi^*(X) \log(\pi(X) + \{1 - \pi^*(X)\} \log \left(\frac{1 - \pi(X)}{1 - \pi^*(X)}\right) \omega(X) \right\}
\]
\[
\leq \mathbb{E}\left\{ \pi^*(X) \left( \frac{\pi(X)}{\pi^*(X)} - 1 \right) \omega(X) + \{1 - \pi^*(X)\} \left( \frac{1 - \pi(X)}{1 - \pi^*(X)} - 1 \right) \omega(X) \right\} = 0,
\]
and the inequality is strict unless \( [\pi(X) - \pi^*(X)] \omega(X) = 0 \) almost surely. If the cure model is identifiable, this cannot happen and thus \( \mathbb{E}\{\ell^*(\theta)\} < \mathbb{E}\{\ell^*(\theta_0)\}, \forall \theta \neq \theta_0. \)

Proof of Lemma 4.1. Define the event
\[
\mathcal{E}_n = \left\{ \sup_{x \in X, \omega(x) > 0} \sup_{y \leq \tau(x)} \hat{S}_C(y - \mid x) - S_C(y - \mid x) \leq (1/2) \inf_{x \in X, \omega(x) > 0} S_C(\tau(x) - \mid x) \right\}.
\]
On the set \( \mathcal{E}_n \), given a measurable function \( \phi(\cdot) \), we can write
\[
\left| \frac{1}{n} \sum_{1 \leq i \leq n} \left[ B_i^*(\hat{S}_C) - B_i^*(S_C) \right] \omega(X_i) \phi(X_i) \right|
\]
\[
\leq \frac{1}{n} \sum_{1 \leq i \leq n} \frac{\Delta_i |\hat{R}_i| \omega(X_i) |\phi(X_i)|}{S_C(Y_i - | X_i) |S_C(Y_i - | X_i) - |\hat{R}_i|}
\]
\[
\leq 2 \sup_{1 \leq i \leq n} |\hat{R}_i| \times \frac{1}{n} \sum_{1 \leq i \leq n} \frac{\omega(X_i) |\phi(X_i)|}{S_C^2(Y_i - | X_i)},
\]
where \( \hat{R}_i = \hat{S}_C(Y_i - | X_i) - S_C(Y_i - | X_i) \). By the preservation of the Glivenko-Cantelli property for classes of functions (see Theorem 3 of van der Vaart and Wellner (2000)), the set of logit transformations of \( \pi(\theta) \) is a \( \mathbb{P}_X \)-Glivenko-Cantelli class of functions of \( X \) with constant envelope, provided Assumptions \( \Box_2 \) and \( \Box_3 \) hold true. The statement follows from the uniform law of large numbers for the empirical process indexed by the set of functions \( \left\{ \omega(\cdot)S_C^2(\cdot - | \cdot)|\log(\pi(\cdot; \theta)/[1 - \pi(\cdot; \theta)]) : \theta \in \Theta \right\} \) with constant envelope, and condition \( \Box_4 \), which implies \( \sup_{1 \leq i \leq n} |\hat{R}_i| = o_P(1) \) and \( \Pr(\mathcal{E}_n) \to 1. \)
Proof of Proposition 4.2. We apply Theorem 5.7 of van der Vaart (2000). First, by construction and Assumption 4.2-3, $\hat{\theta}$ is a well-separated maximum of the map $\theta \mapsto \mathbb{E}\{\ell^*(\theta)\}$, with $\ell^*(\theta)$ defined in equation (3.3). See inequality (3.4). Next, let us note that

$$
\hat{\ell}^*(\theta) - \ell^*(\theta) = \sum_{i=1}^{n} \left[ B^*(\hat{S}_C) - B^*(S_C) \right] \omega(X_i) \log \left( \frac{\pi_i(\theta)}{1 - \pi_i(\theta)} \right).
$$

Since

$$
\sup_{\theta \in \Theta} \left| \hat{\ell}^*(\theta) - \mathbb{E}\{\ell^*(\theta)\} \right| \leq \sup_{\theta \in \Theta} \left| \hat{\ell}^*(\theta) - \ell^*(\theta) \right| + \sup_{\theta \in \Theta} \left| \ell^*(\theta) - \mathbb{E}\{\ell^*(\theta)\} \right|
$$

by our assumptions and the uniform law of large numbers for the empirical process,

$$
\sup_{\theta \in \Theta} \left| \hat{\ell}^*(\theta) - \mathbb{E}\{\ell^*(\theta)\} \right| = o_p(1).
$$

The consistency of $\hat{\theta}$ follows from Theorem 5.7 of van der Vaart (2000).

Proof of Proposition 4.4. By the definition of $\hat{\theta}$ we have the identity $\hat{\ell}^*(\theta)$

$$
0 = \frac{\partial \hat{\ell}^*(\theta)}{\partial \theta} = \frac{\partial \hat{\ell}^*(\theta_0)}{\partial \theta} + \frac{\partial^2 \hat{\ell}^*(\theta)}{\partial \theta \partial \theta} \left( \hat{\theta} - \theta_0 \right)
$$

$$
= \frac{\partial \hat{\ell}^*(\theta_0)}{\partial \theta} + \frac{\partial^2 \hat{\ell}^*(\theta_0)}{\partial \theta \partial \theta} \left( \hat{\theta} - \theta_0 \right) + \left[ \frac{\partial^2 \hat{\ell}^*(\theta)}{\partial \theta \partial \theta} \right] \left( \hat{\theta} - \theta_0 \right),
$$

where $\bar{\theta}$ is some point on the segment between $\hat{\theta}$ and $\theta_0$. Using the definition in equation (3.2) and the short notation $\pi_i(\theta) = \pi(X_i; \theta)$ and $\partial \pi_i(\theta)/\partial \theta = \partial \pi(X_i; \theta)/\partial \theta$, we can write

$$
\frac{1}{n} \frac{\partial \hat{\ell}^*(\theta_0)}{\partial \theta} = \frac{1}{n} \sum_{i=1}^{n} \left[ \frac{B^*_i(\hat{S}_C)}{\pi_i(\theta_0)} - \frac{1 - B^*_i(\hat{S}_C)}{1 - \pi_i(\theta_0)} \right] \omega_i \frac{\partial \pi_i(\theta_0)}{\partial \theta}
$$

$$
= \frac{1}{n} \sum_{i=1}^{n} \frac{B^*_i(S_C) - \pi_i(\theta_0)}{\pi_i(\theta_0)[1 - \pi_i(\theta_0)]} \omega_i \frac{\partial \pi_i(\theta_0)}{\partial \theta} + \frac{1}{n} \sum_{i=1}^{n} \frac{B^*_i(\hat{S}_C) - B^*_i(S_C)}{\pi_i(\theta_0)[1 - \pi_i(\theta_0)]} \omega_i \frac{\partial \pi_i(\theta_0)}{\partial \theta},
$$

and thus, by Assumption 4.5 we have

$$
\frac{1}{n} \frac{\partial \hat{\ell}^*(\theta_0)}{\partial \theta} = \frac{1}{n} \sum_{i=1}^{n} \left\{ \mu(Y_i, \Delta_i, X_i; \theta_0) + \mu^C(Y_i, \Delta_i, X_i; \theta_0) \right\} + o_P(n^{-1/2}).
$$
Next, for any \( \theta \) we have
\[
\frac{1}{n} \frac{\partial^2 \hat{\ell}^*(\theta)}{\partial \theta \partial \theta^\top} = \frac{1}{n} \sum_{i=1}^n \left[ \frac{B_i^*(\hat{S}_C)}{\pi_i^2(\theta)} + \frac{1 - B_i^*(\hat{S}_C)}{[1 - \pi_i(\theta)]^2} \right] \omega_i \frac{\partial \pi_i(\theta)}{\partial \theta} \frac{\partial \pi_i(\theta)}{\partial \theta}^\top + \frac{1}{n} \sum_{i=1}^n \frac{B_i^*(\hat{S}_C) - \pi_i(\theta)}{\pi_i(\theta)[1 - \pi_i(\theta)]} \omega_i \frac{\partial^2 \pi_i(\theta)}{\partial \theta \partial \theta^\top} =: \frac{H_1n(\hat{S}_C; \theta)}{\partial \theta} + \frac{H_2n(\hat{S}_C; \theta)}{\partial \theta}.
\]
Here, \( \frac{\partial^2 \pi_i(\theta)}{\partial \theta \partial \theta^\top} \) denotes the matrix of the second order partial derivatives of \( \pi(X; \theta) \) with respect to \( \theta \). By the preservation of the Glivenko-Cantelli property for classes of functions (see Theorem 3 of [van der Vaart and Wellner (2000)]), and Assumption 4.2-2 and 4.4-3, the sets
\[
\{ \pi(\theta)^{-2} \omega f, \ [1 - \pi(\theta)]^{-2} \omega f : f \in F_{1,kl}, \theta \in \Theta \}
\]
and
\[
\{ \{\pi(\theta)[1 - \pi(\theta)]\}^{-1} \omega g, \ [1 - \pi(\theta)]^{-1} \omega g : g \in F_{2,kl}, \theta \in \Theta \}
\]
with \( F_{1,kl} \) and \( F_{2,kl} \), \( 0 \leq k, l \leq p \), defined in Assumption 4.4-3 are \( \mathbb{P}_\mathcal{X} \)-Glivenko-Cantelli classes of functions of \( X \) with integrable envelope. By Lemma 4.11, deduce that
\[
\sup_{\theta \in \Theta} \left\{ \left| H_{1n}(\hat{S}_C; \theta) - H_{1n}(S_C; \theta) \right| + \left| H_{2n}(\hat{S}_C; \theta) - H_{2n}(S_C; \theta) \right| \right\} = o_P(1).
\]
On the other hand, the uniform law of large numbers for the empirical process yields
\[
\sup_{\theta \in \Theta} \left\{ \left| H_{1n}(S_C; \theta) - \mathbb{E}\{H_{1n}(S_C; \theta)\} \right| + \left| H_{2n}(S_C; \theta) - \mathbb{E}\{H_{2n}(S_C; \theta)\} \right| \right\} = o_P(1).
\]
Lebesgue’s Dominated Convergence Theorem implies
\[
\lim_{\theta \to \theta_0} \mathbb{E}\{H_{1n}(S_C; \theta)\} = \mathbb{E}\{H_{1n}(S_C; \theta_0)\} = A(\theta_0)
\]
and
\[
\lim_{\theta \to \theta_0} \mathbb{E}\{H_{2n}(S_C; \theta)\} = \mathbb{E}\{H_{2n}(S_C; \theta_0)\} = 0.
\]
Gathering facts, deduce
\[
\left\| \frac{\partial^2 \hat{\ell}^*(\theta)}{\partial \theta \partial \theta^\top} - \frac{\partial^2 \hat{\ell}^*(\theta_0)}{\partial \theta \partial \theta^\top} \right\| = o_P(1), \quad (8.1)
\]
and this completes the justification of the representation of \( \hat{\theta} - \theta_0 \). The convergence in law of \( \sqrt{n}(\hat{\theta} - \theta_0) \) is a direct consequence of this representation.

An alternative way to obtain (8.1) is to require that condition (4.1) holds true and impose more regularity on the regression functions in the cure regression model. More
precisely, assume that, in addition to (4.1), there exists an integrable function $C(X)$ and a constant $a > 0$ such that, for any $0 \leq k \leq l \leq p$ and any $\theta, \theta' \in \Theta$,

$$
\omega(x) \left| \frac{\partial^2 \pi}{\partial \theta(k) \partial \theta(l)}(x; \theta) - \frac{\partial^2 \pi}{\partial \theta(k) \partial \theta(l)}(x; \theta') \right| \leq C(x)\|\theta - \theta'\|^a,
$$

and

$$
\omega(x) \left| \left( \frac{\partial \pi}{\partial \theta(k) \partial \theta(l)}(x; \theta) - \frac{\partial \pi}{\partial \theta(k) \partial \theta(l)}(x; \theta') \right)(x; \theta) \right| \leq C(x)\|\theta - \theta'\|^a.
$$

Then the property (8.1) follows using arguments as in the proof of Lemma 4.1.

**Proof of Proposition 4.5.** We follow the lines of the proof of Theorem 4 in Zou (2006). First consider the asymptotic normality part. Let $\theta = \theta_0 + u n^{-1/2}$ and define

$$
\Gamma_n(u) = \hat{u}^* (\theta_0 + u n^{-1/2}) - \lambda \sum_{j=1}^p w_j \left| \theta_{0,(j)} + u_{(j)} n^{-1/2} \right|.
$$

Let $\hat{u} = \arg \max_u \Gamma_n(u)$, such that $\hat{u} = \sqrt{n}(\hat{\theta}_n - \theta_0)$. By Taylor expansion applied to the log-likelihood,

$$
\Gamma_n(u) - \Gamma_n(0) = A_1^{(n)} + A_2^{(n)} + A_3^{(n)} + A_4^{(n)},
$$

where

$$
A_1^{(n)} = \frac{1}{\sqrt{n}} \frac{\partial \hat{u}^* (\theta_0)}{\partial \theta} u
$$

$$
A_2^{(n)} = \frac{1}{2n} u^T \frac{\partial^2 \hat{u}^* (\theta_0)}{\partial \theta \partial \theta^T} u
$$

$$
A_3^{(n)} = \frac{1}{2n} u^T \left[ \frac{\partial^2 \hat{u}^* (\theta_0)}{\partial \theta \partial \theta^T} - \frac{\partial^2 \hat{u}^* (\theta_0)}{\partial \theta \partial \theta^T} \right] u
$$

and

$$
A_4^{(n)} = -\frac{\lambda}{\sqrt{n}} \sum_{j=1}^p w_j \sqrt{n} \left( |\theta_{0,(j)} + u_{(j)} n^{-1/2}| - |\theta_{0,(j)}| \right).
$$

The behavior of $A_1^{(n)}, A_2^{(n)}$ and $A_3^{(n)}$ can be derived from the proof of Proposition 4.4. On the other hand, for $A_4^{(n)}$, by exactly the same arguments as in the proof of Theorem 4 in Zou (2006), we have

$$
\frac{\lambda}{\sqrt{n}} w_j \sqrt{n} \left( |\theta_{0,(j)} + u_{(j)} n^{-1/2}| - |\theta_{0,(j)}| \right) \to \left\{ \begin{array}{ll} 0 & \text{if } \theta_{0,(j)} \neq 0 \\ 0 & \text{if } \theta_{0,(j)} = 0 \text{ and } u_{(j)} = 0 \\ -\infty & \text{if } \theta_{0,(j)} = 0 \text{ and } u_{(j)} \neq 0 \end{array} \right.,
$$

in probability. To summarize, for every $u$, $\Gamma_n(u) - \Gamma_n(0)$ converges in probability to the function

$$
H_n(u) = \left\{ \begin{array}{ll} W_{n, A} u_A - u_A^T A_A(\theta_0) u_A/2 & \text{if } u_{(j)} = 0 \forall j \notin A \\ -\infty & \text{if otherwise} \end{array} \right.,
$$

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where
\[ W_{n,A} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ \mu_A(Y_i, \Delta_i, X_i; \theta_0) + \mu_{A,C}^*(Y_i, \Delta_i, X_i; \theta_0) \right\}. \]

The iid representation, and hence the asymptotic normality for \( u_A \), follows. Moreover, we deduce that \( \hat{u}_{A_c} \to 0 \), in probability.

Next, we investigate the consistency part. It remains to show that \( \forall j' \notin A \), we have \( \Pr(j' \in A_n) \to 0 \). Let us fix arbitrarily \( j' \notin A \) and consider the event \( \{ j' \notin A_n \} \).

Let \( e_{j'} \in \mathbb{R}^{p+1} \) be the vector with zero components, except the \( j' \)th component that is equal to 1. By the Karush-Kuhn-Tucker optimality conditions, we necessarily have
\[
    e_{j'}^\top \frac{\partial \hat{\ell}^*(\hat{\theta}_\lambda)}{\partial \theta} = \lambda w_{j'}.
\]

Thus
\[
    \Pr(j' \in A_n) \leq \Pr \left( e_{j'}^\top \frac{\partial \hat{\ell}^*(\hat{\theta}_\lambda)}{\partial \theta} = \lambda w_{j'} \right).
\]

Next, by Taylor expansion, we could decompose
\[
    \frac{1}{\sqrt{n}} e_{j'}^\top \frac{\partial \hat{\ell}^*(\hat{\theta}_\lambda)}{\partial \theta} = B_1^{(n)} + B_2^{(n)} + B_3^{(n)},
\]
with
\[
    B_1^{(n)} = \frac{1}{\sqrt{n}} e_{j'}^\top \frac{\partial \hat{\ell}^*(\theta_0)}{\partial \theta},
\]
\[
    B_2^{(n)} = \frac{1}{n} e_{j'}^\top \frac{\partial^2 \hat{\ell}^*(\theta_0)}{\partial \theta \partial \theta^\top} \sqrt{n}(\hat{\theta}_\lambda - \theta_0)
\]
and
\[
    B_3^{(n)} = \frac{1}{n} e_{j'}^\top \left[ \frac{\partial^2 \hat{\ell}^*(\theta_\lambda)}{\partial \theta \partial \theta^\top} - \frac{\partial^2 \hat{\ell}^*(\theta_0)}{\partial \theta \partial \theta^\top} \right] \sqrt{n}(\hat{\theta}_\lambda - \theta_0),
\]
with \( \theta_\lambda \) between \( \hat{\theta}_\lambda \) and \( \theta_0 \). By arguments that we have already used, we obtain
\[
    B_1^{(n)} = O_P(1), \quad B_2^{(n)} = O_P(1) \quad \text{and} \quad B_3^{(n)} = o_P(1).
\]

Meanwhile, since \( \sqrt{n}(\hat{\theta} - \theta_0) = O_P(1) \) and \( \lambda n^{\gamma-1/2} \to \infty \),
\[
    \frac{1}{\sqrt{n}} \lambda w_{j'} = \frac{\lambda}{\sqrt{n}} n^{\gamma/2} \frac{1}{\sqrt{n}(\hat{\theta}(j'))} \to \infty, \quad \text{in probability.}
\]

Thus, \( \Pr(j' \in A_n) \to 0 \). Now, the proof is complete. ■
8.2 Uniform convergence and iid representations: examples

In this section we review several approaches for estimating the conditional law of the censoring time used for IPCW in such way that Assumption 4.3 and 4.5 hold true. Namely, we consider nonparametric estimators, such as the Kaplan-Meier and the conditional Kaplan-Meier estimators, and existing estimators in semiparametric models such as proportional hazard, proportional odds and transformation models. For all these models, we propose a guideline to derive iid representations under our assumptions from the existing asymptotic results.

Without loss of generality, we could consider the case of a real-valued function $\varphi(X)$. Recall that we are interested in functions $\varphi$ such that $\omega(x) = 0$ implies $\varphi(x) = 0$. For vector-valued functions it suffices to apply the results presented below for each component. For simplicity, we assume that the sample space $X$ is a subset of a finite-dimensional space. Moreover, we assume $\Pr(T = C) = 0$ and there exists $\tau \in \mathbb{R}$ such that $\Pr(T_0 > \tau) = 0$ and $\inf_{x \in X, \omega(x) > 0} S_C(\tau | x) > 0$.

8.2.1 Kaplan-Meier inverse probability weighting

When the law of the censoring variable $C$ does not depend on the covariates, the survivor function $S_C$ could be estimated by the Kaplan-Meier estimator

$$\hat{S}_C(y) = \prod_{j: Y_j \leq y} \left(1 - \frac{1}{n\{1 - \hat{H}(Y_j-\)}\right)^{1-\Delta_j}, \quad \text{with} \quad n\{1 - \hat{H}(y-)\} = \sum_{j=1}^{n} \mathbb{1}(Y_j \geq t).$$

Here $\hat{H}(y-)$ is left-sided limit of the estimate of marginal distribution function of the observed lifetimes $H(y) = \Pr(Y \leq y), \ y \in \mathbb{R}$. Then the uniform convergence condition (4.1), and thus Assumption 4.3, is guaranteed by the uniform law of large numbers of Stute and Wang (1993).

For Assumption 4.5, one can use the iid representation for the Kaplan-Meier integrals, as stated in Theorem 1.1 of Stute (1996). More precisely, for each $y \in \mathbb{R}$, define

$$\gamma_0(y) = S_C(y-)^{-1}, \quad \gamma_1(y) = \frac{1}{1 - H(y)} \int \mathbb{1}(y < t) \gamma_0(t) \varphi(x) H^{11}(dx, dt),$$

and

$$\gamma_2(y) = \int \int \mathbb{1}(s < y, s < t) \gamma_0(t) \varphi(x) H_0(ds) H^{11}(dx, dt)$$

with $H^{11}(x, y) = \Pr(X \leq x, Y \leq y, \Delta = 1)$. Note that $H^{11}(x, y) = H^{11}(x, \tau), \ \forall y > \tau$. Then Assumption 4.5 holds with

$$\mu_C^\varphi(Y_i, \Delta_i, X_i) = (1 - \Delta_i) \gamma_1(Y_i) - \gamma_2(Y_i), \quad 1 \leq i \leq n.$$
8.2.2 Conditional Kaplan-Meier inverse probability weighting

The conditional Kaplan-Meier estimator, also called Beran estimator (Beran, 1981) is defined as

\[ \hat{S}_C(y \mid x) = \prod_{Y_i \leq y} \left( 1 - \frac{\hat{w}_n(x)}{\sum_{j=1}^{n} \hat{w}_n(x) \mathbb{1}(Y_j \geq Y_i)} \right)^{1-\Delta_i}, \]

where

\[ \hat{w}_n(x) = \frac{K((X_i - x)/b_n)}{\sum_{j=1}^{n} K((X_j - x)/b_n)}, \quad x \in \mathcal{X}. \]

Here, \( b_n \) is a bandwidth sequence and \( K(\cdot) \) is a multivariate kernel function. The uniform law of large numbers of this conditional Kaplan-Meier estimator was established in Corollary 2.1 of Dabrowski (1989) under some regularity conditions on the density of \( X \) and the functions \( x \mapsto \Pr(Y \leq y, \Delta = j \mid X = x) \), \( j = 0, 1, y \leq \tau \). To apply that corollary in our framework, one has to define a set on which the density of the covariate vector stays away from zero and to take the weight function \( \omega(\cdot) \) in the definition of our estimators \( \hat{\theta} \) and \( \hat{\theta}_\lambda \) equal to zero outside this set.

The iid representation of the Kaplan-Meier integrals was extended to conditional Kaplan-Meier integrals, see Lopez (2011). However, the purely nonparametric approach suffers from the course of dimensionality when the sample space \( \mathcal{X} \) is multidimensional. Stronger regularity assumptions and high-order kernels are needed in such cases. For simplicity, following Lopez (2011), assume that \( C \perp X \mid Z \) where \( Z = g(X) \in \mathbb{R} \) with \( g(\cdot) \) a given function. For instance, \( g(X) \) could be a component of \( X \), or a given linear combination of components of \( X \). The case where \( g(\cdot) \) is known up to a finite-dimensional parameter that has to be estimated could be also considered, but it would introduce an additional term in the iid representation in Assumption 4.5 that takes into account the estimation of \( g(\cdot) \). For simplicity, herein we assume that \( g(\cdot) \) is given. Moreover, for some small \( \delta > 0 \), the weight function \( \omega(\cdot) \) vanishes outside the set \( \mathcal{A}_\delta = \{ x \in \mathcal{X} : f_g(g(x)) \geq \delta + \inf_z f_g(z) \} \).

Here, \( f_z \) denotes the density of \( Z = g(X) \), that is supposed to exist and to satisfy some differentiability conditions. Then Beran estimator with the covariate values \( Z_i = g(X_i) \), \( 1 \leq i \leq n \), is defined as

\[ \hat{S}_C(y \mid z) = \prod_{Y_i \leq y} \left( 1 - \frac{\hat{w}_n(z)}{\sum_{j=1}^{n} \hat{w}_n(z) \mathbb{1}(Y_j \geq Y_i)} \right)^{1-\Delta_i}, \quad z \in \mathbb{R}, \]

where

\[ \hat{w}_n(z) = \frac{K((Z_i - z)/a_n)}{\sum_{j=1}^{n} K((Z_j - z)/a_n)}. \]

Here, \( a_n \) is a bandwidth sequence converging to zero as \( n \) tends to infinity, and \( K(\cdot) \) is a univariate kernel function. If the bandwidth \( a_n \) satisfies \( \log(n)n^{-1}a_n^{-3} \rightarrow 0 \) and \( na_n^4 \rightarrow 0 \),

\[ \frac{1}{n} \sum_{1 \leq i \leq n} \left[ \frac{\Delta_i}{S_C(Y_i- \mid Z_i)} - \frac{\Delta_i}{S_C(Y_i- \mid Z_i)} \right] \varphi(X_i) = \frac{1}{n} \sum_{1 \leq i \leq n} \varphi(X_i) \rightarrow 0, \]

and

\[ \frac{1}{n} \sum_{1 \leq i \leq n} \left[ \frac{\hat{S}_C(Y_i- \mid Z_i)}{S_C(Y_i- \mid Z_i)} - 1 \right] \varphi(X_i) \rightarrow 0, \]

as \( n \rightarrow \infty \).
\[
\mu_C^\phi(Y_i, \Delta_i, X_i; \theta_0) = (1 - \Delta_i)\gamma_1(Y_i, Z_i) - \gamma_2(Y_i, Z_i), \quad 1 \leq i \leq n, \tag{8.2}
\]

with
\[
\gamma_0(y, z) = SC(y | z)^{-1}, \quad \gamma_1(y, z) = \frac{1}{1 - H(y | z)} \int 1(y < t)\gamma_0(t, z)\varphi(x)H^{11}(dx, dt | z),
\]
and
\[
\gamma_2(y, z) = \int \int \frac{1(s < y, s < t)\gamma_0(t, z)}{\{1 - H(s | z)^2\}} \varphi(x)H_0(ds | z)H^{11}(dx, dt | z).
\]

Here, \(H_0(y | z) = \Pr(Y \leq y, \delta = 0 | g(X) = z)\) and \(H^{11}(x, y | z) = \Pr(X \leq x, Y \leq y, \delta = 1 | g(X) = z)\).

### 8.2.3 Semiparametric models

In this section we present a general method for guaranteeing Assumption 4.5. This method could be applied to the common semiparametric models used in survival analysis. (For all the models we mention, condition (4.1) is obviously satisfied, and thus Assumption 4.3.)

Assume that the conditions of Lemma 4.1 hold true and \(\varphi(\cdot)\) is bounded. We can write
\[
\frac{1}{n} \sum_{1 \leq i \leq n} \left[ \frac{\Delta_i}{SC(Y_i - | X_i)} - \frac{\Delta_i}{\hat{SC}(Y_i - | X_i)} \right] \varphi(X_i)
= \frac{1 + o_P(1)}{n} \sum_{1 \leq i \leq n} \left\{ q(Y_i, \Delta_i, X_i; SC) - q(Y_i, \Delta_i, X_i; \hat{SC}) \right\}
\]

where for any function \(S\) depending on \(y\) and \(x\) that is càdlàg in \(y\),
\[
q(t, d, x; S) = \frac{d\varphi(x)}{S_C^2(t\, | x)} S(t\, , x).
\]

Then Assumptions 4.5 could be guaranteed in two steps. First, use the equicontinuity of Donsker classes and transform the sum with respect to \(1 \leq i \leq n\) in an expectation with respect to a generic triplet \((Y, \Delta, X)\) given the sample. Next, use the iid representation of \(SC(y - | x)\) such as could be derived in common semiparametric models. For the first step, in the following we introduce a general class of functions for which we prove the Donsker property. For several common semiparametric models and estimators, it could be shown that \(q(\cdot, \cdot, \cdot; SC)\) and \(q(\cdot, \cdot, \cdot; \hat{SC})\) belong to this class with probability tending to 1. For other models, it may be necessary to define an alternative Donsker classes to be used in the first step of the general method we propose herein.

Let us suppose that \(X\) is composed of continuous and discrete components, that is \(X = (X_d^T, X_c^T)^T \in \mathcal{X}_d \times \mathcal{X}_c = \mathbb{R}^{p_d} \times \mathbb{R}^{p_c}\). Then, each vector \(x\) in the support of \(X\) could be split in the subvectors \(x_d \in \mathcal{X}_d\) and \(x_c \in \mathcal{X}_c\). For simplicity, assume that the support \(\mathcal{X}_d\) of the discrete subvector \(X_d\) is finite.
Let $\text{BV}_M[0, \tau]$ be the set of all real-valued càdlàg functions defined on $[0, \tau]$ with the total variation bounded by $M$. Let $\mathcal{C}_M^\alpha(\mathcal{X}_c)$ be the set of all continuous functions $f : \mathcal{X}_c \to \mathbb{R}$ with $\|f\|_\alpha \leq M$, where $\| \cdot \|_\alpha$ is the usual uniform norm defined on the class of functions with uniformly bounded partial derivatives up to order $\alpha$ (the greatest integer smaller than $\alpha$) and whose highest partial derivatives are Lipschitz of order $\alpha - \alpha$. See chapter 2.7.1 in van der Vaart and Wellner (1996). We follow Lopez (2011) and, for $\alpha, M > 0$, define the following class of functions defined on $[0, \tau] \times \mathcal{X}$:

$$
\mathcal{G} = \{(t, x) \mapsto h(t, x) : \forall x, h(\cdot, x) \text{ and } D^k h(\cdot, x) \in \text{BV}_M[0, \tau],
\text{and } \forall t \leq \tau, \forall x_d \in \mathcal{X}_d, h(t, (x_d, \cdot)) \in \mathcal{C}_M^\alpha(\mathcal{X}_c)\},
$$

where for any vector $\mathbf{k} = (k_1, \ldots, k_{p_c})$ of $p_c$ integers, $D^\mathbf{k}$ is the differential operator

$$
D^\mathbf{k} = \frac{\partial^{k_1 + \cdots + k_{p_c}}}{\partial x_{c,1} \cdots \partial x_{c,p_c}}.
$$

The next result shows that $\mathcal{G}$ is a general Donsker class. For this it suffices to show that $\mathcal{G}$ has finite bracketing integral, which here is tantamount to $\int_0^1 \sqrt{\log N_{[\| \cdot \|_\alpha, \mathcal{G}, L_2]}(\varepsilon)} \, d\varepsilon < \infty$, where $N_{[\| \cdot \|_\alpha, \mathcal{G}, L_2]}$ define the $\varepsilon$--bracketing number of the class $\mathcal{G}$ with respect to the $L_2$--norm.

**Lemma 8.4** Assume that $\mathcal{X}_c$ is a bounded, open and convex subset of $\mathbb{R}^{p_c}$ and $\mathcal{X}_d$ is finite. If $M < \infty$ and $\alpha > p_c$, $\mathcal{G}$ is a Donsker class.

**Proof of Lemma 8.4.** We provide a sketch of the proof. The idea is to show that

$$
\log N_{[\| \cdot \|_\alpha, \mathcal{G}, L_\infty]}(\varepsilon) \leq C(1/\varepsilon)^{2p_c/\alpha} \log(1/\varepsilon), \tag{8.3}
$$

for some constant $C$. Since $\int_0^1 (1/\varepsilon)^{p_c/\alpha} \log^{1/2}(1/\varepsilon) d\varepsilon < \infty$ when $p_c/\alpha < 1$, this will guarantee that $\mathcal{G}$ has finite bracketing integral. With a finite set $\mathcal{X}_d$, by the permanence of the Donsker property (see Theorem 2.10.6 in van der Vaart and Wellner (1996)), it suffices to show property (8.4) separately for each value $x_d \in \mathcal{X}_d$. In other words, it suffices to consider that $x = x_c$.

For any $t \in [0, \tau]$, let $\mathcal{G}_t = \{x \mapsto h(t, x) : h \in \mathcal{G}\}$. By Corollary 2.6.2 in van der Vaart and Wellner (1996), for each $t \in [0, \tau]$, we have $\log N_{[\| \cdot \|_\alpha, \mathcal{G}_t, L_2]}(\varepsilon) \leq C_1 \varepsilon^{-p_c/\alpha}$, with $C_1$ a constant depending only on $M, \alpha, \text{diam}(\mathcal{X}_c)$ and $p_c$ (and independent of $t$). Meanwhile, $\log N_{[\| \cdot \|_\alpha, \text{BV}_M[0, \tau], L_\infty]}(\varepsilon) \leq C_2 (1/\varepsilon) \log(1/\varepsilon)$, where $C_2$ is a constant depending only on $M$ and $\tau$. This is a simple bound for the bracketing number that could be obtained by simply building brackets that are piecewise constant on a regular grid. See also the beginning of the proof of Theorem 2.7.5 in van der Vaart and Wellner (1996). In the following, without loss of generality, we consider $M = 1$. To prove (8.3), it suffices to reconsider the proof of Theorem 2.7.1 (and next of Corollary 2.7.2) in van der Vaart and Wellner (1996). More precisely, in the proof of Theorem 2.7.1, replace the entries of the matrices $Af$ by functions of $t$ of total variation bounded by $M$. In van der Vaart and Wellner (1996), the entries of $Af$
are defined for \( f \) ranging over \( \mathcal{C}_1^\infty(\mathcal{X}_c) \) and having the rows built using the values of the partial derivatives of \( f \), up to order equal to the greatest integer strictly smaller than \( \alpha \), discretized on a grid with the mesh controlled by \( \varepsilon \). In our case, such entries could depend also on \( t \) and be taken as a set of brackets covering \( BV_M[0, \tau] \). Deduce a set of brackets that cover \( \mathcal{G} \) and the cardinality of the set of brackets is of order

\[
\exp \left( \{\varepsilon^{-1/\alpha} + \ldots + \varepsilon^{-p/\alpha}\} \log(1/\varepsilon) \right) \varepsilon^{-pc/\alpha}.
\]

Taking the logarithm of the last expression, we recover the bound \((1/\varepsilon)^{2pc/\alpha} \log(1/\varepsilon)\) for the order of the bracketing entropy of \( \mathcal{G} \).

As a first step for guaranteeing Assumption 4.5, using the properties of the model and estimator considered, one could check that

\[
S_C \in \mathcal{G} \quad \text{and} \quad \Pr(\hat{S}_C \in \mathcal{G}) \to 1 \quad (8.4)
\]

in order to deduce, using the permanence properties of Donsker classes, that \( q(\cdot, \cdot, \cdot; S_C) \) and \( q(\cdot, \cdot, \cdot; \hat{S}_C) \) belong to a Donsker class with probability tending to 1. By the asymptotic equicontinuity of Donsker classes, see for instance van der Vaart and Wellner (1996), and our Lemma 8.2, deduce that

\[
\frac{1}{n} \sum_{1 \leq i \leq n} \left[ \frac{\Delta_i}{\Delta_i} - \frac{\Delta_i}{\Delta_i} \right] \varphi(X_i)
\]

where

\[
\mathbb{G}_n(t, x) = \frac{S_C(t- \mid x) - \hat{S}_C(t- \mid x)}{S_C(t- \mid x)}, \quad t \in [0, \tau], x \in \mathcal{X},
\]

and \( F(x, t) = \Pr(X \leq x, T_0 \leq t) \). In the second step, it remains to show that

the process \( \mathbb{G}_n(\cdot, \cdot) \) admits an iid representation \( (8.5) \)

using the properties of the model considered for \( S_C \).

In the following we illustrate the steps (8.4) and (8.5) in several common (semi)parametric models in survival analysis. See Guo and Zeng (2014) for an illuminating survey on semi-parametric models. In these models, the properties of \( \hat{S}_C \) are usually derived from the properties of the conditional cumulative hazard function of \( C \). Note that by the Duhamel identity (Gill and Johansen, 1990), if the conditions of 4.1 hold true, we have

\[
\mathbb{G}_n(t, x) = - \int_{(0,t]} \frac{\hat{S}_C(s- \mid x)}{S_C(s \mid x)} d(\hat{\Lambda}_C - \Lambda_C)(s \mid x)
\]

\[
= -(1 + o(1)) \int_{(0,t]} \frac{S_C(s- \mid x)}{S_C(s \mid x)} d(\hat{\Lambda}_C - \Lambda_C)(s \mid x), \quad t \leq \tau,
\]
where $\Lambda_C(\cdot \mid x)$ is the conditional cumulative hazard function of $C$ given $X = x$ and $\hat{\Lambda}_C(\cdot \mid x)$ is the estimator of $\Lambda_C(\cdot \mid x)$ in the model for $S_C$. When $S_C(\cdot \mid x)$ is continuous,

$$\mathbb{G}_n(t, x) = - \left\{ \hat{\Lambda}_C(t \mid x) - \Lambda_C(t \mid x) \right\} \{1 + o_p(1)\}.$$  

**Parametric models.** One could achieve flexible modeling for $S_C$ using parametric models, such as the Weibull model, where the parameters are replaced by functions of $X$ depending on some unknown vector of coefficients $\beta_C$. In this case, in general, all the survivor functions in the model satisfy the regularity conditions defining the class $\mathcal{G}$, so that condition (8.4) is automatically met. Condition (8.5) follows by Taylor expansion and the asymptotic linear expansions of $\hat{\beta}_C$, the estimator of $\beta_C$ considered. Such asymptotic linear expansions for $\hat{\beta}_C$, based on the so-called influence functions, could be derived for all the common models and estimators $\hat{\beta}_C$.

**Cox’s proportional hazard model.** In this case

$$\Lambda_C(t \mid x) = \exp(x^T \beta_C) \Lambda_{0,C}(t),$$

where $\Lambda_{0,C}(\cdot)$ is the so-called baseline cumulative hazard function. Clearly, $\Lambda_C(t \mid x)$ belongs to $\mathcal{G}$. Any estimate of $\Lambda_C(t \mid x)$ belongs to $\mathcal{G}$ as soon as $\Lambda_{0,C}(\cdot)$ is estimated by a function of total variation bounded by some suitable $\tilde{M}$ depending on $M$, the compact parameter set for $\beta_C$ and the bounded $X$. Next, for any consistent estimator $\hat{\beta}_C$ and uniformly consistent $\hat{\Lambda}_{0,C}(\cdot)$ we could write

$$\mathbb{G}_n(t, x) = - \left\{ \exp(x^T \hat{\beta}_C) \left\{ \hat{\Lambda}_{0,C}(t) - \Lambda_{0,C}(t) \right\} + \Lambda_C(t \mid x)(\hat{\beta}_C - \beta_C) \right\} \{1 + o_p(1)\}.$$  

In the case where $\hat{\beta}_C$ is the maximum partial likelihood estimator and $\hat{\Lambda}_C$ is the associated Breslow estimator, then condition (8.5) follows by the asymptotic results of Andersen and Gill (1982).

**Transformation model.** We consider the class of transformation models investigated by Zeng and Lin (2006), where

$$\Lambda_C(t \mid x) = G \left( \exp(x^T \beta_C) \Lambda_{0,C}(t) \right),$$

where $G(\cdot)$ is a given smooth, strictly increasing transformation function with $G(0) = 0$, $G'(0) > 0$ and $G(\infty) = \infty$. Box-Cox transformations, and logarithmic transformations are two possible examples. Zeng and Lin (2006) extend the partial likelihood idea and the Breslow estimator from Cox’s model and introduce the estimators $\hat{\beta}_C$ and $\hat{\Lambda}_{0,C}$ for which they derive a Gaussian limit. Since

$$\hat{\Lambda}_C(t \mid x) - \Lambda_C(t \mid x) = G \left( \exp(x^T \hat{\beta}_C) \hat{\Lambda}_{0,C}(t) \right) - G \left( \exp(x^T \beta_C) \Lambda_{0,C}(t) \right)$$

$$= G' \left( \exp(x^T \hat{\beta}_C) \hat{\Lambda}_{0,C}(t) \right) \left\{ \exp(x^T \hat{\beta}_C) \hat{\Lambda}_{0,C}(t) - \exp(x^T \beta_C) \Lambda_{0,C}(t) \right\} \{1 + o_p(1)\},$$

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we could easily adapt the arguments used for the case of Cox’s model and, based on
definition of $\hat{\beta}_C$ and $\hat{\Lambda}_0(\cdot)$ and the asymptotic results of Zeng and Lin (2006),
guarantee conditions (8.4) and (8.5).

**Proportional odds model.** In such a model we have

$$S_C(t \mid x) = \frac{\exp(-x^T\hat{\beta}_C)}{H(t) + \exp(-x^T\hat{\beta}_C)},$$

with $H(\cdot)$ some càdlàg function with $H(0) = 0$. See Murphy et al. (1997). Clearly,
$S_C \in \mathcal{G}$ and $\hat{S}_C \in \mathcal{G}$, with $\hat{S}_C(t \mid x) = \exp(-x^T\hat{\beta}_C)/\{H(t) + \exp(-x^T\hat{\beta}_C)\}$, as soon as
$\hat{H}(t) \in BV_{\bar{M}}[0, \tau]$ for some suitable $\bar{M}$. For the required iid representation, we could
use the maximum likelihood estimators for $\beta_C$ and $H(\cdot)$, linearize the expression of $S_C$
with respect to the parameters and use the asymptotic representations of $\sqrt{n}(\hat{H} - H)$
and $\sqrt{n}(\hat{\beta}_C - \beta_C)$ established in the proof of the Theorem 2.2 in Murphy et al. (1997).
That result is established under an additional condition which, in our setup, means that
$\Pr(T_0 = \tau) = \Pr(T_0 \geq \tau) > 0$. This additional technical constraint is quite usual in the
cure regression literature. See, for instance, Lu (2008) and Fang et al. (2003).