



HAL
open science

Regression modelling of interval censored data based on the adaptive ridge procedure

Olivier Bouaziz, Eva Lauridsen, Grégory Nuel

► **To cite this version:**

Olivier Bouaziz, Eva Lauridsen, Grégory Nuel. Regression modelling of interval censored data based on the adaptive ridge procedure. 2018. hal-01959728v1

HAL Id: hal-01959728

<https://hal.science/hal-01959728v1>

Preprint submitted on 20 Dec 2018 (v1), last revised 14 Oct 2020 (v2)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Regression modelling of interval censored data based on the adaptive ridge procedure

Olivier Bouaziz¹, Eva Lauridsen² and Grégory Nuel³

¹Laboratory MAP5, University Paris Descartes and CNRS, Sorbonne Paris Cité, Paris, France

²Ressource Center for Rare Oral Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark

³LPSM, CNRS 7599, 4 place Jussieu, Paris, France

Abstract

We consider the Cox model with piecewise constant baseline hazard to deal with a mixed case of left-censored, interval-censored and right-censored data. Estimation is carried out with the EM algorithm by treating the true event times as unobserved variables. This estimation procedure is shown to produce a block diagonal Hessian matrix of the baseline parameters. Taking advantage of this interesting feature of the estimation procedure a L0 penalised likelihood method is implemented in order to automatically determine the number and locations of the cuts of the baseline hazard. The method is directly extended to the inclusion of exact observations and to a cure fraction. Statistical inference of the model parameters is derived from likelihood theory. Through simulation studies, the penalisation technique is shown to provide a good fit of the baseline hazard and precise estimations of the resulting regression parameters. The method is illustrated on a dental dataset where the effect of covariates on the risk of ankylosis for replanted teeth is assessed.

Keywords: Adaptive Ridge procedure; Interval censoring; Cure model; EM algorithm; Penalised likelihood; Piecewise constant hazard.

1 Introduction

Interval censored data arise in situations where the event of interest is only known to have occurred between two observation times. These types of data are commonly encountered when the patients are intermittently followed up at medical examinations. This is the case for instance in AIDS studies, when HIV infection onset is determined by periodic testing, or in oncology where the time-to-tumour progression is assessed by measuring the tumour size at periodic testing. Dental dataset are another examples which are usually interval-censored because the teeth status of the patients are only examined at visits to the dentist. While interval-censored data are ubiquitous in medical applications it is still a common practice to replace the observation times with their midpoints or endpoints and to consider these data as exact. This allows to analyse the data using standard survival approach (with exact and right-censored data) but may results in a large bias of the estimators.

In the context of interval-censored data, [1] introduced an iterative algorithm for the non-parametric estimation of the survival function. As a different estimation method, the iterative convex minorant was proposed by [2] and [3]. In [2], the authors derived the slow rate of convergence of order $n^{1/3}$ for the non-parametric survival estimator. Moreover, the obtained law is not gaussian and cannot be explicitly computed. Many methods were also developed in a regression setting. In particular, the Cox model with non-parametric baseline was studied in [4].

The authors derived a $n^{1/2}$ convergence rate for the regression parameter with a gaussian limit but the problem of estimation and inference of the baseline survival function pertains in this regression context: the baseline survival function has the $n^{1/3}$ slow rate of convergence and even more problematic, the asymptotic distribution of this function could not be derived. The same conclusions were observed in [5] where the authors use the more general Cox-Aalen model with non-parametric baseline. As a consequence, alternatives to the non-parametric baseline have been introduced. In [6] and [7] parametric baselines such as Weibull or piecewise constant are introduced. In that case, the convergence rate of the global parameters is of order $n^{1/2}$ and the asymptotic distribution is gaussian (see [7]). In [8] a local likelihood is implemented which results in a smooth estimation of the baseline hazard using a kernel function. However, asymptotic properties of the estimators were not derived in their work and the estimators performance depend on the choice of the kernel bandwidth. In [9], monotone B-splines are implemented in order to estimate the cumulative baseline hazard. The authors introduce a two stage data augmentation which allows them to use the Expectation Maximisation algorithm [EM, see 10] in order to perform estimation. Asymptotics with $n^{1/2}$ rate of convergence of the estimators are derived. However, the number and location of the splines knots are pre-determined by the user and the estimators performance depend on the choice of these tuning parameters.

In this work, we study the Cox model with piecewise constant baseline hazard. Treating the unobserved true event times as missing variables we use the EM algorithm to perform estimation. As a result, the Hessian of the log-likelihood to be maximised is seen to be diagonal. This is a remarkable feature of the method that easily allows to perform estimation with the piecewise constant baseline using arbitrarily large set of cuts. In contrast, this model had been already introduced in [11] and [6] but maximisation of the model parameters was achieved using the observed likelihood which resulted in a full rank Hessian matrix. In [11] for example, the authors warn against computational issues which may force the user to reduce the number of cuts by combining adjacent intervals. Using the EM algorithm to perform estimation in the piecewise constant hazard model is new to our knowledge and easy to implement. Also, all the quantities involved in the E-step can be explicitly computed in our method, contrary to previous works (see [8] for example) which require to approximate integrals. In comparison with [9] the E-step is more natural and directly applicable using the complete likelihood. Moreover, taking advantage of the sparse structure of the Hessian matrix, our method can be combined with a L0 penalty designed to detect the location and number of cuts. This is performed through the adaptive ridge procedure, a regularisation method that was introduced in [12], [13] and then applied in a survival context (without covariates) in [14]. This penalisation technique results in a flexible method where the cuts and locations of the piecewise constant baseline are automatically chosen from the data, thus providing a good compromise between purely non-parametric and parametric baseline functions. This is in contrast with existing techniques such as in [9] where the location and number of knots of splines basis are fixed by the user. Finally we also emphasise the advantage of the L0 method in terms of interpretability: by detecting the relevant set of cuts of the baseline the method highlights the different regions of time where the risk of failure varies. This can be of great interest in medical applications in order for the clinicians to precisely detect time intervals of greater risks of failure for example.

Another advantage of using the EM algorithm is to provide direct extensions of the Cox model. In this work we also consider the inclusion of exact data in the estimation method. This mixed case of exact and interval-censored data is usually not easy to analyse as standard methods for interval-censoring do not directly extend to exact data. However, using our method, inclusion of exact data is straightforward through the E-step and the likelihood can be decomposed into the contribution of exact and interval-censored observations. Another extension that is developed in this work is the inclusion of a fraction of non-susceptible patients. This situation is modelled using the cure model of [15] and [16], with a logit link for the probability of being cured. Little attention has been paid to this model in the case of interval-censored data. In [17]

the authors consider a partially linear transformation model where the baseline is modelled using spline basis but the number and location of knots are chosen in an ad-hoc manner. In [18] a different cure model was introduced where the marginal survival function (without conditioning on the susceptible group) is modelled. However, the asymptotic distribution of the estimated parameters were not derived under this model. With our method, estimation in the cure Cox model is straightforward. The E-step results in a weighted log-likelihood with the weights corresponding to the probability of being cured such that our estimation method readily extends to the cure model.

In Section 2 the piecewise constant hazard model is introduced. The estimation method based on the EM algorithm is presented in Section 3 for interval censored data and fixed cuts of the hazard. Estimation in the non-parametric case, in the regression model and extensions for exact data and the cure model are also developed in this section. Then, the L0 penalised likelihood that allows to select the location and number of cuts from the data is presented in Section 4. The construction of confidence intervals and statistical tests is discussed in Section 5. In Section 6, an extensive simulation study is presented where our adaptive ridge estimator is compared with the midpoint estimator and the ICsurv estimator from [9]. Finally, a dental dataset on complications for replanted teeth is analysed in Section 7.

2 A piecewise constant hazard model for interval censored data

Let T denote the time to occurrence of the event of interest. We consider a situation where all individuals are subject to interval censoring defined by the random variables (L, R) such that L and R are observed and $\mathbb{P}(T \in [L, R]) = 1$. The situation $L = 0$ and $R < \infty$ corresponds to left-censoring, $0 < L < R < \infty$ corresponds to strictly interval censoring and $L < R = \infty$ to right censoring. The special case $L = R$ is also allowed which corresponds to exact observations of the time of interest. We introduce a covariate vector Z of dimension d_Z and for convenience we also introduce δ which equals 0 if an individual is right censored and 1 if he/she is exactly observed, left censored or interval censored. The variable T is considered continuous and we assume independent censoring in the following way (see for instance [19]):

$$\mathbb{P}(T \leq t \mid L = l, R = r, Z) = \mathbb{P}(T \leq t \mid l \leq T \leq r, Z).$$

This supposes that the variables (L, R) do not convey additional information on the law of T apart from assuming T to be bracketed by L and R . Finally, we assume non-informative censoring in the sense that the distribution of L and R does not depend on the model parameters involved in the distribution of T .

We consider the following Cox proportional hazard model for the time variable T :

$$\lambda(t \mid Z) = \lambda_0(t) \exp(\beta Z), \tag{1}$$

where β is an unknown row parameter vector of dimension d_Z . We model the baseline function λ_0 through a piecewise constant hazard. Let c_0, c_1, \dots, c_K represent K cuts, with the convention that $c_0 = 0$ and $c_K = +\infty$. Let $I_k(t) = I(c_{k-1} < t \leq c_k)$, with $I(\cdot)$ denoting the indicator function. We suppose that

$$\lambda_0(t) = \sum_{k=1}^K I_k(t) \exp(a_k),$$

for $k = 1, \dots, K$. Under this model, note that the survival and density functions are respectively

equal to:

$$S(t | Z) = \exp \left(- \sum_{k=1}^K e^{a_k + \beta Z} (t \wedge c_k - c_{k-1}) I(c_{k-1} \leq t) \right),$$

$$f(t | Z) = \sum_{k=1}^K I_k(t) \exp \left(a_k + \beta Z - \sum_{j=1}^k e^{a_j + \beta Z} (t \wedge c_j - c_{j-1}) \right).$$

We set $\boldsymbol{\theta} = (a_1, \dots, a_K, \beta)$ the model parameter we aim to estimate. In the following, we will also study the so-called nonparametric situation, when no covariates are available, which is encompassed in our modelling approach as the special case where $Z = 0$. In this context the hazard function is simply equal to λ_0 which is assumed to be piecewise constant and the model parameter is $\boldsymbol{\theta} = (a_1, \dots, a_K)$. The observed data consist of data $= (L_i, R_i, \delta_i)_{1 \leq i \leq n}$ in the nonparametric context and of data $= (L_i, R_i, \delta_i, Z_i)_{1 \leq i \leq n}$ in the regression context, while T_i is considered as incompletely observed. In the latter context, we introduce the notation $a_{i,k} = a_k + \beta Z_i$.

3 Estimation procedure with fixed cuts

For the sake of simplicity, we first consider the scenario when no exact data are observed (which means there only are left, interval and right censored data). The estimation method is based on the EM algorithm and is presented in Section 3.1 in the general regression context since the nonparametric context can be easily derived by setting $Z = 0$. The nonparametric context is discussed in Section 3.2, the implementation of the M step for the regression context is presented in Section 3.3 and the method when exact observations are also available is developed in Section 3.4. Finally, the inclusion of a fraction of non-susceptible individuals is studied in Section 3.5.

3.1 The EM algorithm for left, right and interval censored observations

The observed likelihood is defined with respect to the observed data by:

$$L^{\text{obs}}(\boldsymbol{\theta}) = \prod_{i=1}^n \left\{ \exp \left(- \int_0^{L_i} \lambda_0(t) dt e^{\beta Z_i} \right) \left(1 - \exp \left(- \int_{L_i}^{R_i} \lambda_0(t) dt e^{\beta Z_i} \right) \right) \right\}^{\delta_i}$$

$$\times \left\{ \exp \left(- \int_0^{L_i} \lambda_0(t) dt e^{\beta Z_i} \right) \right\}^{1 - \delta_i}.$$

The Maximum Likelihood Estimator (MLE) can be derived from maximisation of this observed log-likelihood with respect to the model parameters, as in [11] for instance. The obtained parameter estimates are not explicit but a Newton-Raphson algorithm can be easily implemented. However, in this optimisation problem, the block of the Hessian matrix corresponding of the baseline coefficients a_1, \dots, a_K will be of full rank and can lead to intractable solutions if the number of cuts K is large. An alternative method to compute the MLE is therefore to use the EM algorithm based on the complete likelihood of the unobserved true event times. This algorithm will result into a diagonal block matrix of the baseline coefficients.

The EM algorithm is based on the complete likelihood, defined by:

$$L(\boldsymbol{\theta}) = \prod_{i=1}^n f(T_i | Z_i, \boldsymbol{\theta}).$$

Denote by $\boldsymbol{\theta}_{\text{old}}$ the current parameter value. The E-step takes the expectation of the complete log-likelihood with respect to the T_i 's, given the L_i 's, R_i 's, δ_i 's, Z_i 's and $\boldsymbol{\theta}_{\text{old}}$. Write

$$Q_i(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}}) := \mathbb{E}[\log(f(T_i \mid Z_i, \boldsymbol{\theta})) \mid \text{data}, \boldsymbol{\theta}_{\text{old}}] = \int f(t \mid \text{data}, \boldsymbol{\theta}_{\text{old}}) \log f(t \mid Z_i, \boldsymbol{\theta}) dt,$$

where $f(t \mid \text{data}, \boldsymbol{\theta}_{\text{old}})$ represents the conditional density of T_i given data and $\boldsymbol{\theta}_{\text{old}}$, evaluated at t . Under the independent censoring assumption,

$$f(t \mid \text{data}, \boldsymbol{\theta}_{\text{old}}) = \frac{f(t \mid Z_i, \boldsymbol{\theta}_{\text{old}}) I(L_i < t < R_i)}{S(L_i \mid Z_i, \boldsymbol{\theta}_{\text{old}}) - S(R_i \mid Z_i, \boldsymbol{\theta}_{\text{old}})}.$$

The E-step consists of computing the quantity $Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}}) = \sum_i Q_i(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})$. We have:

$$\begin{aligned} Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}}) &= \sum_{i=1}^n \frac{\int_{L_i}^{R_i} f(t \mid Z_i, \boldsymbol{\theta}_{\text{old}}) \log f(t \mid Z_i; \boldsymbol{\theta}) dt}{S(L_i \mid Z_i, \boldsymbol{\theta}_{\text{old}}) - S(R_i \mid Z_i, \boldsymbol{\theta}_{\text{old}})} \\ &= \sum_{i=1}^n \left\{ \frac{1}{S(L_i \mid Z_i, \boldsymbol{\theta}_{\text{old}}) - S(R_i \mid Z_i, \boldsymbol{\theta}_{\text{old}})} \right. \\ &\quad \left. \times \sum_{k=1}^K J_{k,i} \int_{c_{k-1} \vee L_i}^{c_k \wedge R_i} \exp\left(a_{i,k}^{\text{old}} - \sum_{j=1}^k e^{a_{i,j}^{\text{old}}} (t \wedge c_j - c_{j-1})\right) \left(a_{i,k} - \sum_{j=1}^k e^{a_{i,j}^{\text{old}}} (t \wedge c_j - c_{j-1})\right) dt \right\}, \end{aligned}$$

where $J_{k,i}$ is the indicator $I\{(L_i, R_i) \cap (c_{k-1}, c_k) \neq \emptyset\}$ and $a \wedge b$, $a \vee b$ respectively denote $\min(a, b)$, $\max(a, b)$. Now, for $k = 1, \dots, K$, introduce the quantities

$$\begin{aligned} A_{k,i}^{\text{old}} &= \frac{\exp\left(e^{a_{i,k}^{\text{old}}} c_{k-1} + a_{i,k}^{\text{old}} - \sum_{j=1}^{k-1} e^{a_{i,j}^{\text{old}}} (c_j - c_{j-1})\right) J_{k,i} \int_{c_{k-1} \vee L_i}^{c_k \wedge R_i} \exp(-e^{a_{i,k}^{\text{old}}} t) dt}{S(L_i \mid Z_i, \boldsymbol{\theta}_{\text{old}}) - S(R_i \mid Z_i, \boldsymbol{\theta}_{\text{old}})} \\ &= \exp\left(-e^{a_{i,k}^{\text{old}}} c_{k-1} \vee L_i\right) \left(1 - \exp\left(-e^{a_{i,k}^{\text{old}}} (c_k \wedge R_i - c_{k-1} \vee L_i)\right)\right) \\ &\quad \times \frac{\exp\left(e^{a_{i,k}^{\text{old}}} c_{k-1} - \sum_{j=1}^{k-1} e^{a_{i,j}^{\text{old}}} (c_j - c_{j-1})\right) J_{k,i}}{S(L_i \mid Z_i, \boldsymbol{\theta}_{\text{old}}) - S(R_i \mid Z_i, \boldsymbol{\theta}_{\text{old}})} \end{aligned} \quad (2)$$

and

$$\begin{aligned} B_{k,i}^{\text{old}} &= \frac{\exp\left(e^{a_{i,k}^{\text{old}}} c_{k-1} + a_{i,k}^{\text{old}} - \sum_{j=1}^{k-1} e^{a_{i,j}^{\text{old}}} (c_j - c_{j-1})\right) J_{k,i} \int_{c_{k-1} \vee L_i}^{c_k \wedge R_i} (t - c_{k-1}) \exp(-e^{a_{i,k}^{\text{old}}} t) dt}{S(L_i \mid Z_i, \boldsymbol{\theta}_{\text{old}}) - S(R_i \mid Z_i, \boldsymbol{\theta}_{\text{old}})} \\ &= \left\{ \left(\exp(-a_{i,k}^{\text{old}}) + c_{k-1} \vee L_i - c_{k-1} \right) \exp(-e^{a_{i,k}^{\text{old}}} c_{k-1} \vee L_i) \right. \\ &\quad \left. - \left(\exp(-a_{i,k}^{\text{old}}) + c_k \wedge R_i - c_{k-1} \right) \exp(-e^{a_{i,k}^{\text{old}}} c_k \wedge R_i) \right\} \\ &\quad \times \frac{\exp\left(e^{a_{i,k}^{\text{old}}} c_{k-1} - \sum_{j=1}^{k-1} e^{a_{i,j}^{\text{old}}} (c_j - c_{j-1})\right) J_{k,i}}{S(L_i \mid Z_i, \boldsymbol{\theta}_{\text{old}}) - S(R_i \mid Z_i, \boldsymbol{\theta}_{\text{old}})}. \end{aligned} \quad (3)$$

Finally, the M-step corresponds of maximising, with respect to $\boldsymbol{\theta}$, the quantity

$$Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}}) = \sum_{i=1}^n \sum_{k=1}^K \left\{ \left(a_{i,k} - \sum_{j=1}^{k-1} (c_j - c_{j-1}) e^{a_{i,j}^{\text{old}}} \right) A_{k,i}^{\text{old}} - e^{a_{i,k}^{\text{old}}} B_{k,i}^{\text{old}} \right\}.$$

3.2 Estimation in the absence of covariates

In the absence of covariates, the previous results hold with $Z_i = 0$, $a_{i,k} = a_k$ and the model parameters we aim to estimate are just $\boldsymbol{\theta} = (a_1, \dots, a_K)$. The objective function in the M-step can be defined with respect to the sufficient statistics $\bar{A}_k^{\text{old}} = \sum_i A_{k,i}^{\text{old}}$ and $\bar{B}_k^{\text{old}} = \sum_i B_{k,i}^{\text{old}}$:

$$Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}}) = \sum_{k=1}^K \left\{ \left(a_k - \sum_{j=1}^{k-1} (c_j - c_{j-1}) e^{a_j} \right) \bar{A}_k^{\text{old}} - e^{a_k} \bar{B}_k^{\text{old}} \right\}.$$

The derivatives of Q with respect to a_k , $k = 1, \dots, K$, equal

$$\frac{\partial Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k} = \bar{A}_k^{\text{old}} - (c_k - c_{k-1}) e^{a_k} I(k \neq K) \sum_{l=k+1}^K \bar{A}_l^{\text{old}} - e^{a_k} \bar{B}_k^{\text{old}}.$$

As a consequence, in the absence of covariates, one gets the explicit parameters estimators:

$$\exp(\hat{a}_k) = \frac{\bar{A}_k^{\text{old}}}{I(k \neq K) \sum_{l=k+1}^K \bar{A}_l^{\text{old}} (c_k - c_{k-1}) + \bar{B}_k^{\text{old}}}, \quad k = 1, \dots, K,$$

at each step of the EM algorithm. At convergence, this provides an estimator of the hazard function from which quantities of interest, such as the survival function, can be easily derived.

3.3 Estimation in the general regression framework

In the regression framework, each step of the EM algorithm is solved through a Newton-Raphson procedure. The first and second order derivatives of Q with respect to a_k and β are equal to

$$\begin{aligned} \frac{\partial Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k} &= \sum_{i=1}^n \left\{ A_{k,i}^{\text{old}} - (c_k - c_{k-1}) e^{a_k} I(k \neq K) \sum_{l=k+1}^K A_{l,i}^{\text{old}} e^{\beta Z_i} - e^{a_k} B_{k,i}^{\text{old}} e^{\beta Z_i} \right\}, \\ \frac{\partial Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial \beta} &= \sum_{i=1}^n Z_i \sum_{l=1}^K \left(A_{l,i}^{\text{old}} - \left\{ \sum_{j=1}^{l-1} (c_j - c_{j-1}) e^{a_j} A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_l} B_{l,i}^{\text{old}} e^{\beta Z_i} \right\} \right), \end{aligned}$$

and

$$\begin{aligned} \frac{\partial^2 Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k^2} &= - \sum_{i=1}^n \left\{ (c_k - c_{k-1}) e^{a_k} I(k \neq K) \sum_{l=k+1}^K A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_k} B_{k,i}^{\text{old}} e^{\beta Z_i} \right\}, \\ \frac{\partial^2 Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial \beta^2} &= - \sum_{i=1}^n Z_i Z_i^t \sum_{l=1}^K \left(\sum_{j=1}^{l-1} (c_j - c_{j-1}) e^{a_j} A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_l} B_{l,i}^{\text{old}} e^{\beta Z_i} \right), \\ \frac{\partial^2 Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k \partial \beta} &= - \sum_{i=1}^n Z_i \left((c_k - c_{k-1}) e^{a_k} I(k \neq K) \sum_{l=k+1}^K A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_k} B_{k,i}^{\text{old}} e^{\beta Z_i} \right). \end{aligned}$$

The block matrix of the Hessian corresponding to the second order derivatives with respect to the a_k 's is diagonal while the three other blocks are of full rank. Inversion of the Hessian matrix is then achieved using the Schurr complement which takes advantage of this sparse structure of the Hessian. When considering a large number of cuts, that is $K \gg d_Z$, the total complexity of the inversion of the Hessian is of order $\mathcal{O}(K)$. The exact formula of the Schurr complement is given in the Appendix section.

3.4 Inclusion of exact observations

It is straightforward to deal with exact observations since they can be directly included in the EM algorithm. For an exact observation i ,

$$\mathbb{E}[\log(f(T_i | Z_i; \boldsymbol{\theta})) | \text{data}, \boldsymbol{\theta}_{\text{old}}] = \log(f(T_i | Z_i; \boldsymbol{\theta})) = \sum_{k=1}^K \{O_{i,k} a_{i,k} - \exp(a_{i,k}) R_{i,k}\},$$

with $O_{i,k} = I(c_{k-1} < T_i < c_k)$ and $R_{i,k} = T_i \wedge c_k - c_{k-1}$. Note that this corresponds to the classical contribution of an exact observation to the log-likelihood in the standard Poisson regression for right censored observations (see for instance [20]). As a result, Q can be decomposed as

$$\begin{aligned} Q(\boldsymbol{\theta} | \boldsymbol{\theta}_{\text{old}}) = & \sum_{i \text{ not exact}} \sum_{k=1}^K \left\{ \left(a_{i,k} - \sum_{j=1}^{k-1} (c_j - c_{j-1}) e^{a_{i,j}} \right) A_{k,i}^{\text{old}} - e^{a_{i,k}} B_{k,i}^{\text{old}} \right\} \\ & + \sum_{i \text{ exact}} \sum_{k=1}^K \left\{ O_{i,k} a_{i,k} - \exp(a_{i,k}) R_{i,k} \right\}. \end{aligned}$$

The estimation method follows as previously. In particular, in the absence of covariates, the explicit parameters estimator of (a_1, \dots, a_K) are equal to:

$$\exp(\hat{a}_k) = \frac{\bar{A}_k^{\text{old}} + \bar{O}_k}{I(k \neq K) \sum_{l=k+1}^K \bar{A}_l^{\text{old}} (c_k - c_{k-1}) + \bar{B}_k^{\text{old}} + \bar{R}_k}, k = 1, \dots, K,$$

where $\bar{O}_k = \sum_{i \text{ exact}} \bar{O}_{i,k}$ and $\bar{R}_k = \sum_{i \text{ exact}} \bar{R}_{i,k}$.

In the regression setting, maximisation over the β and a_1, \dots, a_K parameters is performed through the Newton-Raphson algorithm as before. Full expressions of the score vector and Hessian matrix are given in the Appendix section. The Schurr complement is used again to inverse the Hessian matrix (see the Appendix section).

3.5 Inclusion of a fraction of non-susceptibles (cure fraction)

Taking into account non-susceptible individuals is possible using the cure model from [15]. This is achieved by modelling the latent status (susceptible/non-susceptible) of the individuals through a variable Y which equals 1 for patients that will eventually experience the event and 0 for patients that will never experience the event. Since the estimation method uses the EM algorithm, this latent variable can be easily dealt with through the E-step.

The probability of being susceptible is equal to $p = \mathbb{P}[Y = 1]$. For a right censored individual, Y is not observed. The marginal survival function of T is $S(t) = (1 - p) + pS(t | Y = 1)$ for $t < \infty$, where $S(t | Y = 1)$ is the survival function of the susceptibles. Note that $S(t) \rightarrow 1 - p$ as $t \rightarrow \infty$. We assume that censoring is independent of Y . See [15] for more details about the cure model. The proportional hazard Cox model for the susceptibles is defined as

$$\lambda(t | Y = 1, Z) = \lambda_0(t) \exp(\beta Z). \quad (4)$$

The cure model specifies the hazard, conditional on Y and Z , to be equal to $\lambda(t | Y, Z) = Y\lambda(t | Y = 1, Z)$. The baseline function λ_0 is assumed to be piecewise constant as in Section 2 and the conditional density and survival functions of the susceptibles are respectively noted $f(t | Y = 1, Z)$ and $S(t | Y = 1, Z)$. If one wants to model the effect of covariates on the probability of being cured, a logistic link can be used:

$$p(X) = \mathbb{P}[Y = 1 | X] = \frac{\exp(\gamma X)}{1 + \exp(\gamma X)}, \quad (5)$$

where X is a covariate vector including the intercept and γ is a row parameter vector, both of dimension d_X . The observed data then consist of data $= (L_i, R_i, \delta_i, Z_i, X_i)_{1 \leq i \leq n}$ while T_i and Y_i are respectively incompletely observed and non observed data. The model parameter is $\theta = (a_1, \dots, a_L, p)$ in the completely nonparametric context (no covariates X nor Z), $\theta = (a_1, \dots, a_L, \beta, p)$ if only the covariate Z is used or $\theta = (a_1, \dots, a_L, \beta, \gamma)$ in the full regression context (with covariates X and Z). In the later case, we introduce the notation $p_i = \mathbb{P}[Y_i = 1 | X_i]$. The other situations are encompassed in our modelling approach by setting $X = 0$ and/or $Z = 0$. Note that our cure model is identifiable and does not require additional constraints such as in [15] where the authors had to impose $S(t | Y = 1, Z)$ to be null for t greater than the last event time in the context of exact and right-censored data.

Under the cure model, the observed likelihood is now defined as

$$\begin{aligned} L^{\text{obs}}(\theta) &= \prod_{i=1}^n \left\{ p_i \exp\left(-\int_0^{L_i} \lambda_0(t) dt e^{\beta_0 Z_i}\right) \left(1 - \exp\left(-\int_{L_i}^{R_i} \lambda_0(t) dt e^{\beta_0 Z_i}\right)\right) \right\}^{\delta_i} \\ &\quad \times \left\{ (1 - p_i) + p_i \exp\left(-\int_0^{L_i} \lambda_0(t) dt e^{\beta_0 Z_i}\right) \right\}^{1 - \delta_i} \end{aligned}$$

and the complete likelihood is defined as

$$L(\theta) = \prod_{i=1}^n p_i^{Y_i} (1 - p_i)^{1 - Y_i} \prod_{i=1}^n \{f(T_i | Y_i = 1, Z_i; \theta)\}^{Y_i}.$$

The E step is performed as follows. Let $\pi_i^{\text{old}} = \mathbb{E}[Y_i | \text{data}, \theta_{\text{old}}]$, we have:

$$\pi_i^{\text{old}} = \delta_i + \frac{(1 - \delta_i) p_{\text{old}} S(L_i | Y_i = 1, Z_i, \theta_{\text{old}})}{1 - p_{\text{old}} + p_{\text{old}} S(L_i | Y_i = 1, Z_i, \theta_{\text{old}})}.$$

The E-step consists of computing the function $Q(\theta | \theta_{\text{old}}) = \mathbb{E}[\log(L(\theta)) | \text{data}, \theta_{\text{old}}]$. In the case of interval-censored and exact observations, we have:

$$\begin{aligned} Q(\theta | \theta_{\text{old}}) &= \sum_{i=1}^n \left\{ \pi_i^{\text{old}} \log(p_i) + (1 - \pi_i^{\text{old}}) \log(1 - p_i) \right\} \\ &\quad + \sum_{i \text{ not exact}} \pi_i^{\text{old}} \sum_{k=1}^K \left\{ \left(a_{i,k} - \sum_{j=1}^{k-1} (c_j - c_{j-1}) e^{a_{i,j}} \right) A_{k,i}^{\text{old}} - e^{a_{i,k}} B_{k,i}^{\text{old}} \right\} \\ &\quad + \sum_{i \text{ exact}} \sum_{k=1}^K \left\{ O_{i,k} a_{i,k} - \exp(a_{i,k}) R_{i,k} \right\}, \end{aligned}$$

where $A_{k,i}^{\text{old}}, B_{k,i}^{\text{old}}$ are defined as in Equations (2) and (3) with the quantity $S(\cdot | Z_i, \theta_{\text{old}})$ replaced by $S(\cdot | Y_i = 1, Z_i, \theta_{\text{old}})$. The terms $O_{i,k}$ and $R_{i,k}$ were defined in Section 3.4.

The Q function separates the terms with γ and the terms involving (a_1, \dots, a_K, β) such that maximisation of these terms can be performed separately. Let $\bar{A}_k^{\pi, \text{old}} = \sum_i \pi_i^{\text{old}} A_{k,i}^{\text{old}}$, $\bar{B}_k^{\pi, \text{old}} = \sum_i \pi_i^{\text{old}} B_{k,i}^{\text{old}}$ and $\bar{\pi}^{\text{old}} = \sum_i \pi_i^{\text{old}}$. In the nonparametric setting, explicit estimators of the parameters can be computed at each step of the EM algorithm through the formulas:

$$\begin{aligned} \hat{p} &= \frac{\bar{\pi}^{\text{old}}}{n}, \\ \exp(\hat{a}_k) &= \frac{\bar{A}_k^{\pi, \text{old}} + \bar{O}_k}{I(k \neq K) \sum_{l=k+1}^K \bar{A}_l^{\pi, \text{old}} (c_k - c_{k-1}) + \bar{B}_k^{\pi, \text{old}} + \bar{R}_k}, k = 1, \dots, K. \end{aligned}$$

In the general regression context, a Newton-Raphson procedure is implemented separately to maximise both parts of Q . The first and second order derivatives of Q with respect to γ are equal to:

$$\begin{aligned}\frac{\partial Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial \gamma} &= \sum_{i=1}^n X_i \left(\pi_i^{\text{old}} - \frac{\exp(\gamma X_i)}{1 + \exp(\gamma X_i)} \right), \\ \frac{\partial^2 Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial \gamma^2} &= - \sum_{i=1}^n X_i X_i^t \frac{\exp(\gamma X_i)}{(1 + \exp(\gamma X_i))^2}.\end{aligned}$$

Exact expressions of the first and second order derivatives of Q with respect to a_k and β are given in the Appendix section. They are expressed as weighted versions with respect to π_i^{old} of the derivatives obtained in the context where all individuals are susceptible. As previously, the block matrix corresponding to the second order derivatives with respect to the a_k s of the Hessian is diagonal and inversion of the Hessian matrix is achieved using the Schurr complement.

4 Estimation procedure using the adaptive ridge method

In this section we present a penalised estimation method to detect the number and location of the cuts of the baseline hazard, when those are not known in advance. The proposed methodology is based on the work of [12], [13] and [14] and can be applied to any of the previous scenarios (with exact observations, with a cure fraction, in a nonparametric setting, in a regression setting) where the function Q represents the objective function associated with the context under study.

4.1 A penalised EM algorithm

If the number of cuts is not known in advance, we choose a large grid of cuts (i.e K large) and we penalise the log-likelihood in the manner of [12], [13] and [14]. This penalisation is designed to force consecutive values of the a_k s to be close to each other. It is defined in the following way:

$$\ell(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}}) = Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}}) - \frac{\text{pen}}{2} \sum_{k=1}^{K-1} w_k (a_{k+1} - a_k)^2, \quad (6)$$

where $\boldsymbol{w} = (w_1, \dots, w_{K-1})$ are non-negative weights that will be iteratively updated in order for the weighted ridge penalty term to approximate the L0 penalty. The pen term is a tuning parameter that describes the degree of penalisation. Note that the two extreme situations pen= 0 and pen= ∞ respectively correspond to the unpenalised log-likelihood model of Section 3 and to the Cox model with exponential baseline.

Only the maximisation over (a_1, \dots, a_K) is affected by the penalty. The first and second order derivatives of ℓ with respect to a_1, \dots, a_K are equal to:

$$\begin{aligned}\frac{\partial \ell(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k} &= \frac{\partial Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k} + (w_{k-1} a_{k-1} - (w_{k-1} + w_k) a_k + w_k a_{k+1}) \text{pen}, \\ \frac{\partial^2 \ell(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k^2} &= \frac{\partial^2 Q(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k^2} - (w_{k-1} + w_k) \text{pen}, \\ \frac{\partial^2 \ell(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k \partial a_{k+1}} &= \frac{\partial^2 \ell(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_{k+1} \partial a_k} = w_k \text{pen}, \\ \frac{\partial^2 \ell(\boldsymbol{\theta} \mid \boldsymbol{\theta}_{\text{old}})}{\partial a_k \partial a_{k'}} &= 0 \text{ for } k, k' \text{ such that } |k - k'| \geq 2.\end{aligned}$$

The block matrix corresponding to the second order derivatives with respect to the a_k s is therefore tridiagonal. For a given value of pen and of the weight vector \boldsymbol{w} , inversion of the

Hessian matrix is performed using the Schurr complement as previously (see the Appendix section) and the Newton-Raphson algorithm is implemented to derive $\hat{\boldsymbol{\theta}}$. Once the Newton-Raphson algorithm has reached convergence, the weights are updated at the l th step from the equation

$$w_k^{(l)} = \left((\hat{a}_{k+1}^{(l)} - \hat{a}_k^{(l)})^2 + \varepsilon^2 \right)^{-1},$$

for $k = 1, \dots, K-1$ with $\varepsilon = 10^{-5}$ (recommended value from [12]) and where the $\hat{a}_k^{(l)}$'s represent the estimates of the a_k 's obtained through the Newton-Raphson algorithm. This form of weights is motivated by the fact that $w_k(a_{k+1} - a_k)^2$ is close to 0 when $|a_{k+1} - a_k| < \varepsilon$ and close to 1 when $|a_{k+1} - a_k| > \varepsilon$. Hence the penalty term tends to approximate the L0 norm. The weights are initialized by $w_k^{(0)} = 1$, which gives the standard ridge estimate of \mathbf{a} .

Finally, for a given value of pen, once the adaptive ridge algorithm has reached convergence, a set of cuts is found for the \hat{a}_k 's verifying $w_k(\hat{a}_{k+1} - \hat{a}_k)^2 > 0.99$. The non-penalised log-likelihood Q is then maximised using this set of cuts and the final maximum likelihood estimate is derived using the results of Section 3. It is important to stress that the penalised likelihood is used only to select a set of cuts. Reimplementing the non-penalised log-likelihood Q in the final step enables to reduce the bias classically induced by penalised maximisation techniques.

4.2 Choice of the penalty term

A Bayesian Information Criterion (BIC) is introduced in order to choose the penalty term. As explained in the previous section, for each penalty value the penalised EM likelihood (6) selects a set of cuts. For a selected set of cuts we denote by m the total number of parameters to be estimated and by $\hat{\boldsymbol{\theta}}_m$ the corresponding non-penalised estimated model parameter obtained by maximisation of the Q function. The BIC is then defined as:

$$\text{BIC}(m) = -2 \log(L^{\text{obs}}(\hat{\boldsymbol{\theta}}_m)) + m \log(n).$$

Note that the BIC is expressed here in terms of selected models. Since different penalty values can yield the same selection of cuts, the BIC needs only to be computed for all different selected models (and not for all different penalties). As an illustration of the model selection procedure, a full regularisation path can be produced where for each penalty value corresponds a set of cuts and parameter estimates, see for example Figure 3 of [14]. The final set of cuts along with its estimator $\hat{\boldsymbol{\theta}}_{\hat{m}}$ is chosen such that $\text{BIC}(\hat{m})$ is minimal.

Other criteria could be used to perform model selection such as the Akaike Information Criterion (AIC). However we recommend to use the BIC as this criterion was shown to have similar performance as the cross-validation criterion on time to event data in [14].

4.3 Discussion on computational aspects

The complexity for the inversion of the Hessian of ℓ is still of order $\mathcal{O}(K)$, in the case $K \gg d_X + d_Z$ (see the Appendix section on the Schurr complement for details about computational complexity). However, for a given penalty, it should be noted that the global algorithm for maximising Q or ℓ consists of an EM algorithm with a Newton-Raphson procedure at each step. As a consequence, a Generalised Expectation Maximisation (GEM) algorithm (see [10]) is used instead of the standard EM where, as soon as the value of Q or ℓ increases, the Newton-Raphson procedure is stopped. This results in computing only a few steps of the Newton-Raphson algorithm (very often only one step is needed). As the EM algorithm is usually very slow to reach convergence the `turboEM` R package with the `squareEM` option is used to accelerate the procedure (see for instance [21]). Finally, the algorithm must be iterated for the whole sequence of penalties. In order to evaluate the global computational cost, numerical

experiments were conducted which showed that, for a maximum of K_{\max} initial cuts, the total complexity of the whole procedure is of order $\mathcal{O}(nK_{\max}^{1/2})$. See Section 6.3 for more details on these aspects.

5 Statistical inference

Inference on the model parameters can be achieved after selection of the cuts of the baseline function by considering these cuts as fixed parameters. Then the problem reduces to a fully parametric model. Theoretical results for parametric models with interval censored data have been discussed in [7] for instance.

Statistical tests are implemented from the likelihood ratio test which is based on the observed likelihood L^{obs} . Let $\boldsymbol{\theta} = (\theta_1, \theta_2)$ with θ_1 of dimension d . To test the null hypothesis $H_0 : \theta_1 = \theta_0$, with θ_0 known, one can use the test statistic $-2 \log(L^{\text{obs}}(\theta_0, \hat{\theta}_2)/L^{\text{obs}}(\hat{\theta}_1, \hat{\theta}_2))$ which follows a chi-squared distribution with d degrees of freedom from standard likelihood theory. Confidence intervals can also be constructed from the likelihood ratio statistic. Let us assume that $\boldsymbol{\theta} = (\theta_1, \theta_2)$ with θ_1 of dimension 1 and consider the test $H_0 : \theta_1 = \theta_0$ versus $H_1 : \theta_1 \neq \theta_0$. The $1 - \alpha$ confidence interval level of the parameter θ_1 will be determined by the set of values θ_0 such that the previous test is not significant at the significance level α . Note that the p-value of the test is defined by (with a slight abuse of notation for the realisation of the test statistic)

$$\mathbb{P} \left[\chi^2(1) > -2 \log \left(\frac{L^{\text{obs}}(\theta_0, \hat{\theta}_2)}{L^{\text{obs}}(\hat{\theta}_1, \hat{\theta}_2)} \right) \right],$$

and the test is non-significant if this value is greater than α . Let $q_{\chi^2}^{1-\alpha}$ be the $1 - \alpha$ quantile of the $\chi^2(1)$ distribution. The bounds of the confidence intervals can therefore be determined by resolving the equation

$$\log(L^{\text{obs}}(\theta_0, \hat{\theta}_2)) + \frac{1}{2} q_{\chi^2}^{1-\alpha} - \log(L^{\text{obs}}(\hat{\theta}_1, \hat{\theta}_2)) = 0, \quad (7)$$

with respect to θ_0 . This equation has two solutions and since it is clear that $\theta_0 = \hat{\theta}_1$ is part of the confidence interval (the p-value equals one for this value), a grid search can be performed using for example the `uniroot` package with the two starting intervals $[\hat{\theta}_1 - c; \hat{\theta}_1]$ and $[\hat{\theta}_1; \hat{\theta}_1 + c]$, where c is a positive constant. This constant can be chosen arbitrarily large and should satisfy that the left-hand side of Equation (7) is of opposite sign for $\theta_0 = \hat{\theta}_1 - c$ and $\theta_0 = \hat{\theta}_1 + c$. See [22] for more details about the likelihood ratio test approach for constructing confidence intervals.

A more classical method for deriving confidence intervals is based on the normal approximation of the model parameter. It requires to compute the Hessian matrix of the observed log-likelihood $\partial^2 \log(L^{\text{obs}}(\boldsymbol{\theta}))/\partial \boldsymbol{\theta}^2$ evaluated at $\boldsymbol{\theta} = \hat{\boldsymbol{\theta}}$. This can be done by direct calculation or by using the following relationship which makes use of the complete likelihood:

$$\frac{\partial \log(L^{\text{obs}}(\boldsymbol{\theta}))}{\partial \boldsymbol{\theta}} = \mathbb{E} \left[\frac{\partial \log(L(\boldsymbol{\theta}))}{\partial \boldsymbol{\theta}} \mid \text{data}, \boldsymbol{\theta} \right]. \quad (8)$$

In the above equation, the Hessian can be computed based on the complete likelihood by taking the derivative of the right-hand side of the equation with respect to $\boldsymbol{\theta}$. Note that, in the absence

of exact observations and of a cure fraction,

$$\begin{aligned}\log(\mathbf{L}(\boldsymbol{\theta})) &= \sum_{i=1}^n \sum_{k=1}^K I(c_{k-1} < T_i \leq c_k) \left(a_{i,k} - \sum_{j=1}^k e^{a_{i,j}} (T_i \wedge c_j - c_{j-1}) \right), \\ \frac{\partial \log(\mathbf{L}(\boldsymbol{\theta}))}{\partial a_k} &= \sum_{i=1}^n \left\{ I(c_{k-1} < T_i \leq c_k) - \sum_{l=k}^K I(c_{l-1} < T_i \leq c_l) e^{a_{i,k}} (T_i \wedge c_k - c_{k-1}) \right\}, \\ \frac{\partial \log(\mathbf{L}(\boldsymbol{\theta}))}{\partial \beta} &= \sum_{i=1}^n \sum_{k=1}^K I(c_{k-1} < T_i \leq c_k) Z_i \left(1 - \sum_{j=1}^k e^{a_{i,j}} (T_i \wedge c_j - c_{j-1}) \right).\end{aligned}$$

We now need to take the expectation conditionally on the data of the last two equations. This will involve the quantities

$$\mathbb{P}[c_{k-1} < T_i \leq c_k \mid \text{data}, \boldsymbol{\theta}] = \frac{S(c_{k-1} \vee L_i \mid Z_i, \boldsymbol{\theta}) - S(c_k \wedge R_i \mid Z_i, \boldsymbol{\theta})}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})},$$

and

$$\begin{aligned}\mathbb{E}[I(c_{k-1} < T_i \leq c_k) T_i \mid \text{data}, \boldsymbol{\theta}] &= J_{k,i} \int_{c_{k-1} \vee L_i}^{c_k \wedge R_i} t \exp\left(a_{i,k} - \sum_{j=1}^k e^{a_{i,j}} (t \wedge c_j - c_{j-1})\right) dt \times \frac{1}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})}, \\ &= \left\{ \left(\exp(-a_{i,k}) + c_{k-1} \vee L_i \right) \exp(-e^{a_{i,k}} c_{k-1} \vee L_i) - \left(\exp(-a_{i,k}) + c_k \wedge R_i \right) \exp(-e^{a_{i,k}} c_k \wedge R_i) \right\} \\ &\quad \times \frac{\exp\left(e^{a_{i,k}} c_{k-1} - \sum_{j=1}^{k-1} e^{a_{i,j}} (c_j - c_{j-1})\right) J_{k,i}}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})}.\end{aligned}$$

Calculation of the right-hand side of Equation (8) is now straightforward. The Hessian is finally obtained by taking the derivative with respect to $\boldsymbol{\theta}$ of this quantity. The explicit expression of this quantity is given in the Appendix section.

The normal approximation method can be tedious to implement due to the calculation of the Hessian matrix. On the other hand the likelihood ratio test approach does not suffer this drawback and is easy to implement as long as the parameter of interest is of dimension one. Finally, bootstrap methods can be implemented to derive confidence intervals. This technique is particularly interesting when the interest lies in the estimation of the survival function in a non-parametric or regression context. In order to derive the asymptotic distribution of such functional one would need to use the delta-method which may result in very complicated formula for the variance estimator. The bootstrap alternative avoids these technicalities.

6 Simulation study

In this section we study the performance of the proposed estimators on simulated data.

6.1 Two scenarios with exact, left, interval-censored and right-censored data

We first consider the Cox regression setting of Equation (1) where the aim is to correctly estimate the regression coefficient β and the baseline function λ_0 . We set the baseline as a piecewise constant function with three cuts in the following way:

$$\lambda_0(t) = \begin{cases} 0.5 \times 10^{-2} & \text{for } t \in (0, 20], \\ 1 \times 10^{-2} & \text{for } t \in (20, 40], \\ 2 \times 10^{-2} & \text{for } t \in (40, 50], \\ 4 \times 10^{-2} & \text{for } t > 50. \end{cases}$$

The covariate vector Z is of dimension $d_Z = 2$ with the first component simulated as a Bernoulli variable with parameter 0.6 and the second component is independently simulated as a uniform variable with parameters $[0, 2]$. The regression parameter is equal to $\beta = (\log(2), \log(0.8))^t$. The values of L_i and R_i were determined through a visit process defined in the following way. Let \mathcal{U} denote the uniform distribution. Two visits were simulated such that the first one $V_1 \sim \mathcal{U}[0, 60]$ and the other one $V_2 = V_1 + \mathcal{U}[0, 120]$. Then the observations for which $T_i < V_1$ correspond to left-censored observations with $L_i = 0$ and $R_i = V_1$, the observations for which $T_i > V_2$ correspond to right-censored observations with $L_i = V_2$ and $R_i = \infty$, and the observations for which $V_1 < T_i < V_2$ correspond to strictly interval-censored observations with $L_i = V_1$ and $R_i = V_2$. This simulation setting corresponds to Scenario S1 and gave a proportion of 25% of left-censored observations, 52% of interval-censored observations and 23% of right-censored observations. In Scenario S2, 18% of exact observations were first sampled and then the same simulation scheme for the visit process was used. The percentage of left, interval and right censored observations remains identical under this scenario. Note that the two simulation settings produce very wide censoring intervals. As a result it is particularly challenging for our method to recover the true baseline hazard with the correct cuts and estimated values. As a matter of fact, when looking at strictly interval-censored observations only, the average width of the interval $\mathbb{E}[R_i - L_i]$ is equal to 60.

Our adaptive ridge estimator was constructed from a grid of cuts ranging from $c_0 = 10$ to $c_{17} = 90$, with all cuts equally spaced of size 5. The set of penalty terms was taken, on the log scale, as the set of 200 equally spaced values ranging from $\log(0.1)$ to $\log(10\,000)$. For the EM algorithm, the a_k and β parameters were initialised to 0. As described in Section 4, the BIC was used to find an estimated set of cuts and the non penalised estimator was reimplemented with this set of cuts in order to derive our final estimator. This estimator was compared with the midpoint estimator and the ICsurv estimator from [9]. The midpoint estimator consists of replacing the interval-censored observations by their midpoint $(L_i + R_i)/2$. The data then consist of exact and right-censored observations and can be dealt with by implementing the standard Cox regression estimators. The ICsurv estimator models the cumulative baseline function using monotone splines and uses a two-stage data augmentation method to perform estimation through the EM algorithm. This estimator is implemented using the ICsurv package. Following the guidelines from [9] this estimator was computing using basis splines having degree 3 with 5 interior knots placed evenly across the range of endpoints of the observed intervals. The β parameters and the spline coefficients were respectively initialised to 0 and 1. A very fine grid of time was used for the calculation of the cumulative baseline hazard from time 0 to time 200 with a step equal to 0.1. This estimator cannot include exact observations and is computed only for the scenario S1.

A total of $M = 500$ replications were implemented and the bias and the empirical standard error (SE) of $\hat{\beta}$ were computed for each estimator. In order to assess the quality of estimation of λ_0 , the baseline survival function $S_0(t) = \exp(-\int_0^t \lambda_0(u)du)$ was also estimated with each estimator. Then, as a measure of precision, the Integrated Mean Squared Error (MISE) was decomposed as $\text{MISE}(\hat{S}_0) = \text{IBias}^2(\hat{S}_0) + \text{IVar}(\hat{S}_0)$, where

$$\begin{aligned} \text{IBias}^2(\hat{S}_0) &= \int_0^{60} \left(\frac{1}{M} \sum_{m=1}^M \hat{S}_0^{(m)}(u) - S_0(u) \right)^2 du, \\ \text{IVar}(\hat{S}_0) &= \frac{1}{M} \sum_{m=1}^M \int_0^{60} \left(\hat{S}_0^{(m)}(u) - \frac{1}{M} \sum_{m'=1}^M \hat{S}_0^{(m')}(u) \right)^2 du. \end{aligned}$$

The $\hat{S}_0^{(m)}$, $m = 1, \dots, M$, represent the estimates for each replication. Finally, the total variation between $\hat{\lambda}_0$ and λ_0 was also computed for our adaptive ridge estimator. For a given estimate

$\hat{\lambda}_0^{(m)}$, the following quantity was computed

$$\text{TV}^{(m)}(\hat{\lambda}_0^{(m)}) = \sum_{k=1}^K (c_k - c_{k-1}) |\exp(\hat{a}_k) - \exp(a_k)|,$$

and the average over all estimates $\text{TV}(\hat{\lambda}_0) = \sum_m \text{TV}^{(m)}(\hat{\lambda}_0^{(m)})/M$ was reported. The results are presented in Tables 1 and 2 for Scenarios S1 and S2. Three different sample sizes ($n = 200, 400, 1000$) were considered in the two scenarios, for the midpoint, the ICsurv and the adaptive ridge estimators.

From the simulation results, it is seen that the midpoint and ICsurv estimates have a lower variance than our adaptive ridge estimator both for $\hat{\beta}$ and \hat{S}_0 . However, the midpoint estimator is systematically biased and this bias does not get smaller as the sample size increases. The ICsurv also exhibits a strong bias which slightly decreases for large sample sizes. On the other hand, our estimator always has the smallest bias and both the bias and the variance decrease as the sample size increases. For example, in Scenario S1 for $n = 400$, which corresponds to the sample size of the real data analysis of Section 7 and to similar proportions of left, interval and right censoring, our estimator exhibits a bias for $\beta = (\log(2), \log(0.8))^t$ that is 15 and 19 times smaller than the bias from the midpoint estimator and 12 and 2.6 times smaller than the bias from the ICsurv estimator. For the estimation of S_0 our estimator bias is more than 40 times smaller than the midpoint estimator and more than 35 times smaller than the ICsurv estimator. In terms of MSE, our estimator and the ICsurv estimators show comparable performance for the estimation of β while for the estimation of \hat{S}_0 our estimator outperforms the ICsurv estimator. In Scenario S2 the effect of adding exact observations is seen to decrease the bias and variance of all estimators, for both estimation methods (midpoint and adaptive ridge). For $n = 400$ the bias for our estimator of β is divided by 4 and 15 and the bias for our estimator of S_0 is divided by 3.

The performance of the BIC to detect the correct number of cuts was also assessed in the simulation experiments. As previously noticed our simulation experiment generates very wide intervals which makes it difficult for the estimation method to correctly recover the number of cuts. As a result the BIC tends to over-penalise the estimator in this simulation setting. For example in Scenario S1, for $n = 1000$, the BIC chose a model with only two cuts in 56% of the simulated experiments, it chose a model with only one cut in 40% of the simulated experiments and it chose the correct model with three cuts in only 4% of the simulated experiments. Other simulation settings were considered. In particular, our estimator was seen to perform much better in a setting with 14 visits such that $V_1 \sim \mathcal{U}[0, 20]$ and $V_j = V_{j-1} + \mathcal{U}[0, 10]$, for $j = 2, \dots, 14$. In that case, for $n = 1000$, our estimator chose the correct model with three cuts in 82% of cases. The total variation of $\hat{\lambda}_0$ was equal to 0.191 in this setting, a value that must be compared with 0.416, the total variation that was obtained in Scenario 1. The performance of the other parameter estimates ($\hat{\beta}$ and \hat{S}_0) were also much better in this setting (results not shown).

6.2 Two scenarios that include exact observations and a cure fraction

We now consider two new scenarios which include a proportion of non-susceptible individuals. For the susceptibles, the data include left, interval and right-censored observations along with a proportion of exact observations. The model is defined by Equations (4) and (5) with a logistic link for the probability of being cured. In both scenarios, the Z covariate, β coefficient and λ_0 baseline function are all generated as in Section 6.1. The X covariate is of dimension $d_X = 2$ (including the intercept) and follows a Bernoulli distribution with parameter 0.8. In Scenario S3, $\gamma = (\log(2.35), \log(2))^t$ and in Scenario S4, $\gamma = (\log(0.8), \log(2))^t$. These values yield an average number of susceptible individuals $\mathbb{E}[p(X)]$ respectively equal to 80% and 58%. Among the susceptibles, both scenarios correspond to a proportion of 18% of exact observations, 19% of

Table 1: Simulation results for the estimation of β in Scenarios S1 and S2 with 100% of susceptible individuals. S1: no exact data, 25% of left-censoring, 52% of interval-censoring, 23% of right-censoring. S2: 18% of exact data, 19% of left-censoring, 40% of interval-censoring, 23% of right-censoring.

	n	Adaptive Ridge estimate			Midpoint estimate			ICsurv estimate		
		Bias($\hat{\beta}$)	SE($\hat{\beta}$)	MSE($\hat{\beta}$)	Bias($\hat{\beta}$)	SE($\hat{\beta}$)	MSE($\hat{\beta}$)	Bias($\hat{\beta}$)	SE($\hat{\beta}$)	MSE($\hat{\beta}$)
S1	200	0.032	0.235	0.056	-0.174	0.184	0.064	-0.158	0.175	0.056
		-0.010	0.181	0.033	0.057	0.141	0.023	0.050	0.149	0.025
	400	0.012	0.166	0.028	-0.177	0.127	0.047	-0.148	0.119	0.036
		-0.014	0.120	0.015	0.050	0.096	0.012	0.037	0.101	0.012
	1 000	0.007	0.099	0.010	-0.171	0.075	0.035	-0.135	0.071	0.023
		-0.003	0.075	0.006	0.056	0.062	0.007	0.035	0.063	0.005
S2	200	0.033	0.213	0.047	-0.128	0.181	0.049			
		-0.006	0.169	0.029	0.045	0.147	0.024			
	400	0.003	0.153	0.023	-0.138	0.128	0.035			
		-0.001	0.119	0.014	0.046	0.104	0.013			
	1 000	0.006	0.092	0.009	-0.136	0.078	0.025			
		0.002	0.071	0.005	0.051	0.062	0.006			

Table 2: Simulation results for the estimation of S_0 in Scenarios S1 and S2 with 100% of susceptible individuals. S1: no exact data, 25% of left-censoring, 52% of interval-censoring, 23% of right-censoring. S2: 18% of exact data, 19% of left-censoring, 40% of interval-censoring, 23% of right-censoring.

	n	Adaptive Ridge estimate			Midpoint estimate		ICsurv estimate	
		IBias ² (\hat{S}_0)	IVar(\hat{S}_0)	TV($\hat{\lambda}_0$)	IBias ² (\hat{S}_0)	IVar(\hat{S}_0)	IBias ² (\hat{S}_0)	IVar(\hat{S}_0)
S1	200	0.002	0.266	0.784	0.124	0.122	0.129	0.254
	400	0.003	0.138	0.600	0.124	0.061	0.107	0.129
	1 000	0.002	0.059	0.416	0.126	0.023	0.100	0.052
S2	200	0.001	0.196	0.646	0.074	0.114		
	400	0.001	0.103	0.484	0.074	0.060		
	1 000	0.000	0.038	0.277	0.075	0.022		

left observations, 40% of interval-censored observations and 23% of right-censored observations. The results are presented in Table 3. Only our adaptive ridge estimator has been implemented for these two scenarios. The γ estimator is initialised to 0 in the EM algorithm.

A slight deterioration of the variance estimation of $\hat{\beta}$ and $\hat{\lambda}_0$ is seen when a cure fraction is included and the degree of deterioration increases as the proportion of cured gets bigger. On the other hand the bias of the parameter estimates is similar with or without the cure fraction. In the presence of a cure fraction, the γ parameter is less accurately estimated as compared to the β parameter both in terms of bias and variance. Nevertheless the results show that as the sample size increases the bias and variance of $\hat{\gamma}$ get smaller with a bias very close to 0 for a sample size equal to 1 000. The estimation performance of $\mathbb{E}[p(X)]$ was also investigated by computing the average value of $\sum_i \hat{p}(X_i)/n$ for all generated samples where $\hat{p}(X)$ is defined as in Equation (5) with γ replaced by $\hat{\gamma}$. For example, in Scenario S4 we found a bias and empirical standard error (SE) equal for $n = 200$ to 0.057 (SE = 0.064), for $n = 400$ to 0.046 (SE = 0.044) and for $n = 1 000$ to 0.033 (SE = 0.028).

More simulations were conducted. In particular, the cure model without covariates for the cure fraction was also implemented in Scenario S1 such that the parameters to be estimated are $\theta = (a_1, \dots, a_L, \beta, p)$ with the true value of p equal to 1. In replications of samples of size 400, it was seen that the model estimated the proportion of susceptibles p to a value greater than 0.99 in 98% of cases and the lowest value on the 500 replications for the estimation of p was equal to 0.95. This highlights the very high specificity of our model in terms of detecting a cure fraction. It shows that our model does not tend to overestimate the proportion of cured when the population is homogeneous, which is a very important feature of the estimation method.

On the other hand, a scenario identical to Scenario S1 but with a true proportion of susceptibles equal to $p = 0.7$ was also considered. In replications of samples of size 400, the estimator of p was equal to 0.712 on average and only 0.5% of the estimates were greater than 0.99. This suggests in turn a high sensitivity of our model to detect heterogeneity in interval censored data. Simulations under different true hazards were also considered, such as the Weibull distribution. The performance of our estimator, the ICsurv and midpoint estimators was similar and the results are therefore omitted here.

Table 3: Simulation results for the estimation of β and S_0 in Scenarios S3 and S4. S3: 80% of susceptible individuals. S4: 58% of susceptible individuals. Among the susceptible individuals, 18% of exact data, 19% of left-censoring, 40% of interval-censoring, 23% of right-censoring.

		Adaptive Ridge estimate								
	n	Bias($\hat{\beta}$)	SE($\hat{\beta}$)	MSE($\hat{\beta}$)	Bias($\hat{\gamma}$)	SE($\hat{\gamma}$)	MSE($\hat{\gamma}$)	IBias $^2(\hat{S}_0)$	IVar(\hat{S}_0)	TV($\hat{\lambda}_0$)
S3	200	-0.015	0.291	0.085	0.102	0.498	0.259	0.004	0.324	0.840
		0.003	0.236	0.056	0.011	0.630	0.398			
	400	-0.017	0.207	0.043	0.075	0.356	0.132	0.002	0.160	0.659
		-0.005	0.162	0.026	0.027	0.433	0.189			
	1 000	0.006	0.127	0.016	0.025	0.184	0.035	0.001	0.059	0.414
		0.006	0.094	0.009	0.012	0.198	0.039			
S4	200	-0.021	0.387	0.150	0.077	0.479	0.235	0.005	0.563	1.195
		-0.010	0.310	0.096	0.038	0.511	0.262			
	400	-0.023	0.255	0.066	0.048	0.296	0.090	0.003	0.255	0.810
		0.003	0.209	0.044	0.016	0.309	0.096			
	1 000	-0.009	0.150	0.023	0.032	0.186	0.036	0.001	0.096	0.530
		0.008	0.124	0.015	0.004	0.205	0.042			

6.3 Computational cost of the adaptive ridge algorithm

The computation time for the method was evaluated on replicated samples for the three sample sizes $n = 200, 400, 1\,000$ and for different values of the maximal number of initial cuts: $K_{\max} = 18, 40, 80$. We estimated the implementation of the whole method with 200 penalty values and using the `turboEM` R package with the `squareEM` option (see for instance [21]) in order to accelerate the EM algorithm, to $0.0016 \times n K_{\max}^{1/2}$ minutes. For example, for $n = 400, K_{\max} = 40$ the whole program takes 4 minutes, for $n = 400, K_{\max} = 80$ it takes 5.7 minutes, for $n = 1\,000, K_{\max} = 40$ it takes 10.12 minutes and for $n = 1\,000, K_{\max} = 80$ it takes 14.3 minutes. These values are given as an indication of the algorithmic complexity and should be considered with caution as the implementation has not been optimised. In particular, computation of the $A_{k,i}^{\text{old}}$ and $B_{k,i}^{\text{old}}$ terms could be improved by computing the set of values $(c_k \wedge R_i, c_{k-1} \vee L_i)$ such that $(L_i, R_i) \cap (c_{k-1}, c_k) \neq \emptyset$ more efficiently in C++. Also the non-penalised MLE is implemented for each selection of cuts. For small penalty values, the set of selected cuts can be quite large and the `turboEM` R package has trouble to converge in these cases. For very large set of selected cuts it often does not converge at all and the algorithm is stopped after 200 iterations. This procedure could be greatly improved by only implementing the MLE for reasonable sets of cuts.

Finally, it should be noted that the adaptive ridge procedure needs only to be implemented once on the dataset, in order to detect the set of cuts. Then given this set of cuts, the piecewise-constant hazard model is much faster to compute. For example in Scenario S1 with three cuts, the computation time of the piecewise-constant hazard maximum likelihood model is on average respectively equal to 1.13, 1.80 and 3.33 seconds for $n = 200, 400, 1\,000$.

7 Ankylosis complications for replanted teeth on a dental dataset

The method is illustrated on a dental dataset. 322 patients with 400 avulsed and replanted permanent teeth were followed-up prospectively in the period from 1965 to 1988 at the university hospital in Copenhagen, Denmark. The following replantation procedure was used: the avulsed tooth was placed in saline as soon as the patient was received at the emergency ward. If the tooth was obviously contaminated, it was cleansed with gauze soaked in saline or rinsed with a flow of saline from a syringe. The tooth was replanted in its socket by digital pressure. The patients were then examined at intermittent visits to the dentist. In this study, we focused on a complication called ankylosis characterized by the fusion of the tooth to the bone such that the variable of interest T is the time from replantation of the tooth to ankylosis. This complication may occur if the cells on the root surface is damaged in which case, healing of the periodontal ligament surrounding the tooth will be impaired, leading to local ingrowth of bone. Ankylosis cannot be arrested and gradually the root of the tooth will be replaced by bone which will eventually lead to tooth loss. The data are described in great details in [23].

A total of 28% of the data were left censored, 35.75% were interval censored and 36.25% were right censored. Four covariates were included in the study: the stage of root formation (72.5% of mature teeth, 27.5% of immature teeth), the length of extra-alveolar storage (mean time is 30.9 minutes), the type of storage media (85.25% physiologic, 14.75% non physiologic) and the age of the patient (the mean age for mature teeth is 16.81 years). There is no need for a cure fraction in this analysis since all different models (non-parametric or regression models) estimated the cure fraction to 0%. The adaptive ridge method found four cuts for the baseline hazard at time points 100, 500, 800 and 900 where the initial grid search was composed of 10 spaced time points from 0 to 200 and then of 100 spaced time points from 200 to 2000 ($K_{\max} = 40$). The initial grid search was motivated by the data: for 71% of the left and interval-censored data, the right endpoint is lower than 200.

Non-parametric survival estimates were first computed, one for the whole population and two for each subgroup defined by the stage of root formation (see Figure 1). Confidence intervals were also computed using the bootstrap method with 500 replications. These plots illustrate an interesting feature of the adaptive ridge procedure: by selecting a parsimonious set of cuts, the method highlights the different regions of time where the risk of failure varies. There is in particular a very high risk of ankylosis before 100 days as shown by the very steep survival curve on this time interval. On the global survival curve, the risk of developing ankylosis (one minus the survival function) before 100 days is estimated to 48.35% [43.39%; 53.67%]. Then the slope of the survival curve decreases from 100 days to 500 days, with a risk to develop ankylosis before 500 days estimated to 59.94% [54.96%; 64.57%]. The risk of ankylosis after 900 days is almost null (as shown by the plateau of the survival curve) suggesting that if a patient has not yet developed ankylosis after 900 days he/she is almost no longer at risk for this complication.

When looking at the two subgroups defined by stage of root formation we can see that the risk of ankylosis is much higher in the mature group than in the immature group. This is a very interesting result as it confirms the finding from [24] where periodontal ligament healing was seen to be less frequent with advanced stages of root development. From our analysis, it is seen that the risk is in particular higher in the interval [100, 500] for the mature group than for the immature group, with ankylosis coming mostly from the mature group in this time range. For the immature group, the risk of developing ankylosis before 100 days is estimated to 35.54% [26.85%; 45.13%] and to 52.84% [46.26%; 59.03%] for the mature teeth. Then the slope of the survival curve decreases from 100 days to 500 days, with a risk to develop ankylosis before 500 days estimated to 38.74% [28.97%; 47.62%] for the immature teeth and to 67.92% [62.36%; 73.31%] for the mature teeth. The risk gets very low after 500 days for all groups.

Finally a Cox model was implemented with all the covariates included. Since age shows little variation for immature teeth, this last variable was only included in interaction with the stage

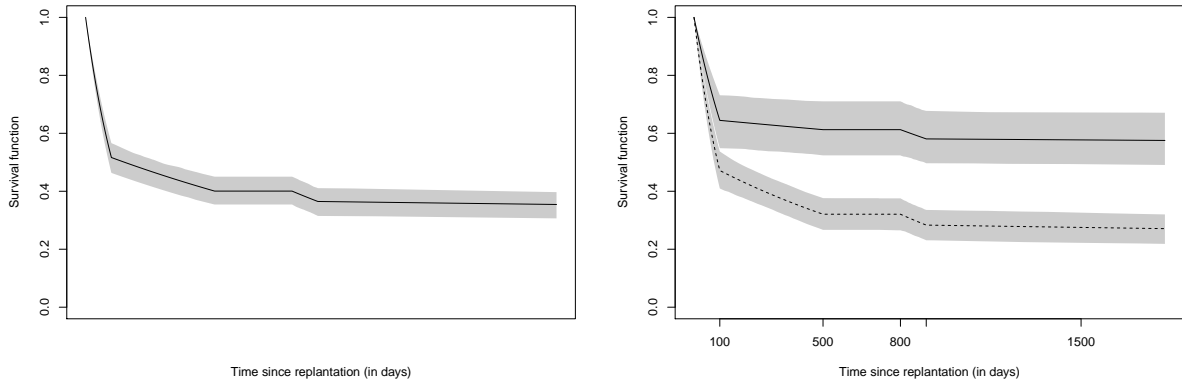


Figure 1: On the left panel, estimate of the survival function of time to ankylosis for the whole population. On the right panel, estimates of the survival function for the immature teeth (solid line) and for the mature teeth (dotted lines). Confidence intervals are plotted along the curves in shaded areas using the bootstrap approach.

Covariates	HR	95% CI	p-value
Mature	2.00	[1.74; 2.29]	1.89×10^{-5}
Storage time (hours)	1.23	[1.11; 1.34]	0.0017
Physiologic storage	0.93	[0.81; 1.06]	0.6980
Age>20 (mature teeth)	1.27	[0.99; 1.61]	0.1272

Table 4: Regression modelling of time to ankylosis on the dental dataset (HR: Hazard Ratio, CI: Confidence Interval). The adaptive ridge found four cuts for the baseline hazard at times 100, 500, 800 and 900.

of root formation such that the baseline value corresponds to immature teeth and the covariate is defined as age greater than 20 years for mature teeth only. The results for the effects of the covariates are shown in Table 4. Statistical tests and confidence intervals for each variable were implemented using the log-ratio statistic test as explained in Section 5. It can be seen that the stage of root formation is highly significant with a two-fold increased risk for mature teeth to develop ankylosis. The storage time is also highly significant with a 1.23 increase of risk per hour. The type of storage media seems to have no effect on ankylosis and age is not significant even at the 10% level. The baseline hazard values along with their 95% confidence intervals are also displayed in Table 5. This hazard corresponds to the risk of immature teeth with non-physiologic type of storage and a storage time of 20 minutes. We can see how the risk is much higher before 100 days than at any other time period. Prediction curves for any specific individual can be plotted using these values.

Cuts	$\exp(\hat{a}_k) \times 10^3$	95% CI $\times 10^3$
(0, 100]	3.71	[3.19; 4.28]
(100, 500]	0.39	[0.28; 0.52]
(500, 800]	0.00	[0.00; 0.00]
(800, 900]	0.62	[0.31; 1.07]
(900, $+\infty$)	0.02	[0.01; 0.04]

Table 5: Baseline hazard from the regression modelling of time to ankylosis on the dental dataset (CI: Confidence Interval). This hazard corresponds to the risk of immature teeth with non-physiologic type of storage and a storage time of 20 minutes.

8 Conclusion

The estimation method proposed in this paper is very general and allows to deal with a wide range of situations. We first introduced the method for the mixed case of left-censored, interval-censored and right-censored data and we then directly extended it to consider the inclusion of exact observations and a cure fraction. We showed that treating the true event times as unobserved and using the EM algorithm to perform estimation resulted in a diagonal block matrix of the baseline hazard in the piecewise constant Cox model. This is a very interesting feature of our approach since the standard estimation method for this model (see for instance [7]) results in a full rank Hessian matrix, which can pose some serious computational problems for a moderate number of baseline cuts. Moreover, this allowed us to use the L0 penalisation technique developed in [12] and [13] which was also implemented for exact and right censored data in [14]. Starting from a large grid of baseline cuts this penalisation technique forces two similar adjacent values to be equal. This results in a very flexible model since the location and number of cuts of the baseline are directly determined from the data. As compared to the ICsurv method from [9], the EM algorithm is readily applicable without need of a data augmentation step. Even though our cumulative baseline hazard does not result in a smooth function as compared to their spline approach, our method was shown to perform greatly on simulated data and even to outperform the method from [9] especially in terms of bias of the estimated parameters. On the dental dataset we also showed the interesting feature of the adaptive ridge procedure: by detecting the different time regions where the hazard for ankylosis changes, it revealed a very high risk of failure from replantation of the tooth until 100 days after replantation and a risk near to zero after 900 days.

By use of a logit link we developed the general cure model introduced by [15] and [16], for interval-censored data. From this model the effect of covariates on the odds of being cured and on the hazard risk of the susceptibles can be assessed. Interestingly, the combination of the piecewise constant baseline hazard and the adaptive ridge procedure produce a very flexible model in this context and avoids the use of arbitrary constraints such as in [15] where the authors had to require that the conditional survival function is set to zero beyond the last event time.

Another type of heterogeneity could be modelled with the use of frailty models (see [25] for instance). The EM approach for frailty models could then be used as a direct extension of our estimation method. However, it would require to compute the conditional value of the frailty variable given the observed data, a work that is left to future research. Similarly the standard mixture problem where one assumes the population to be composed of two (or more) subgroups with different hazards could be considered (see for instance [26] for this model in a high dimensional setting). The use of the piecewise constant baseline hazard would be crucial for this problem as the model is only identifiable for parametric baselines. The implementation of the adaptive ridge procedure would then result in a very flexible model for this problem.

9 Appendix

9.1 The Schurr complement

The Schurr complement is used to compute the inverse of the Hessian matrix of Q , in the case of fixed cuts (Section 3) and of l , for the adaptive ridge estimator (Section 4). It makes use of the special structure of the block matrix corresponding to the second order derivatives with respect to the a_k s which is either diagonal (for Q) or tri-diagonal (for l).

Let $\mathcal{I}(a, \beta)$ be minus the Hessian matrix of Q or l for the maximisation problem with respect to a_1, \dots, a_L and $\beta_1, \dots, \beta_{d_Z}$. Let A be of dimension $K \times K$, B of dimension $K \times d_Z$ and C be of dimension $d_Z \times d_Z$ such that

$$\mathcal{I}(a, \beta) = \begin{pmatrix} A & B \\ B^t & C \end{pmatrix}$$

Let $U(a, \beta)$ be the score vector of Q or l and b_1 be the column vector of dimension K , b_2 be the column vector of dimension d_Z such that $U(a, \beta) = (b_1, b_2)^t$. Using the Schurr complement, we have

$$\mathcal{I}(a, \beta)^{(-1)}U(a, \beta) = \begin{pmatrix} A^{-1}b_1 - A^{-1}B(C - B^tA^{-1}B)^{-1}(b_2 - B^tA^{-1}b_1) \\ (C - B^tA^{-1}B)^{-1}(b_2 - B^tA^{-1}b_1) \end{pmatrix}.$$

For the inversion of the Hessian matrix of Q and l , the $K \times K$ matrix A is either diagonal (for Q) or a band matrix of bandwidth equal to 1 (for l). Its inverse can be efficiently computed using a fast C++ implementation of the LDL algorithm. This is achieved in linear complexity using the R `bandsolve` package. As a result, the total complexity for the computation of $\mathcal{I}(a, \beta)^{(-1)}U(a, \beta)$ is of order $\mathcal{O}(K)$ in the case $K \gg d_Z$.

9.2 Score vector and Hessian matrix for the function Q when including exact observations and a cure fraction

In the presence of exact observations and a cure fraction, the score vector and the Hessian matrix are given from the following formulas:

$$\begin{aligned} \frac{\partial Q(\boldsymbol{\theta} | \boldsymbol{\theta}_{\text{old}})}{\partial a_k} &= \sum_{i \text{ not exact}} \pi_i^{\text{old}} \left\{ A_{k,i}^{\text{old}} - (c_k - c_{k-1})e^{a_k} I(k \neq K) \sum_{l=k+1}^K A_{l,i}^{\text{old}} e^{\beta Z_i} - e^{a_k} B_{k,i}^{\text{old}} e^{\beta Z_i} \right\} \\ &\quad + \sum_{i \text{ exact}} \left\{ O_{i,k} - \exp(a_k + \beta Z_i) R_{i,k} \right\}, \\ \frac{\partial Q(\boldsymbol{\theta} | \boldsymbol{\theta}_{\text{old}})}{\partial \beta} &= \sum_{i \text{ not exact}} \pi_i^{\text{old}} Z_i \sum_{l=1}^K \left(A_{l,i}^{\text{old}} - \left\{ \sum_{j=1}^{l-1} (c_j - c_{j-1}) e^{a_j} A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_l} B_{l,i}^{\text{old}} e^{\beta Z_i} \right\} \right) \\ &\quad + \sum_{i \text{ exact}} Z_i \sum_{l=1}^K \left\{ O_{i,l} - \exp(a_l + \beta Z_i) R_{i,l} \right\}, \end{aligned}$$

and

$$\begin{aligned} \frac{\partial^2 Q(\boldsymbol{\theta} | \boldsymbol{\theta}_{\text{old}})}{\partial a_k^2} &= - \sum_{i \text{ not exact}} \pi_i^{\text{old}} \left\{ (c_k - c_{k-1})e^{a_k} I(k \neq K) \sum_{l=k+1}^K A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_k} B_{k,i}^{\text{old}} e^{\beta Z_i} \right\} \\ &\quad - \sum_{i \text{ exact}} \exp(a_k + \beta Z_i) R_{i,k}, \\ \frac{\partial^2 Q(\boldsymbol{\theta} | \boldsymbol{\theta}_{\text{old}})}{\partial \beta^2} &= - \sum_{i \text{ not exact}} \pi_i^{\text{old}} Z_i Z_i^t \sum_{l=1}^K \left(\sum_{j=1}^{l-1} (c_j - c_{j-1}) e^{a_j} A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_l} B_{l,i}^{\text{old}} e^{\beta Z_i} \right) \\ &\quad - \sum_{i \text{ exact}} Z_i Z_i^t \sum_{l=1}^K \exp(a_l + \beta Z_i) R_{i,l}, \\ \frac{\partial^2 Q(\boldsymbol{\theta} | \boldsymbol{\theta}_{\text{old}})}{\partial a_k \partial \beta} &= - \sum_{i \text{ not exact}} \pi_i^{\text{old}} Z_i \left((c_k - c_{k-1})e^{a_k} I(k \neq K) \sum_{l=k+1}^K A_{l,i}^{\text{old}} e^{\beta Z_i} + e^{a_k} B_{k,i}^{\text{old}} e^{\beta Z_i} \right), \\ &\quad - \sum_{i \text{ exact}} Z_i \exp(a_k + \beta Z_i) R_{i,k}. \end{aligned}$$

9.3 Score vector and Hessian matrix for the observed log-likelihood

For simplicity, the formulas are given in the absence of cure fraction. In order to compute the score $\partial \log(L^{\text{obs}}(\boldsymbol{\theta}))/\partial \boldsymbol{\theta}$ we use the relation (8) and we separate exact and non exact observations in the following way:

$$\frac{\partial \log(L^{\text{obs}}(\boldsymbol{\theta}))}{\partial \boldsymbol{\theta}} = \sum_{i \text{ not exact}} \frac{\partial L_{i,1}^{\text{obs}}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} + \sum_{i \text{ exact}} \frac{\partial L_{i,2}^{\text{obs}}(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}.$$

For the non-exact observations, we introduce

$$C_{i,k}(\boldsymbol{\theta}) = \frac{S(c_{k-1} \vee L_i | Z_i, \boldsymbol{\theta}) - S(c_k \wedge R_i | Z_i, \boldsymbol{\theta})}{S(L_i | Z_i, \boldsymbol{\theta}) - S(R_i | Z_i, \boldsymbol{\theta})},$$

$$D_{i,k}(\boldsymbol{\theta}) = J_{k,i} \left\{ (\exp(-a_{i,k}) + c_{k-1} \vee L_i) \exp(-e^{a_{i,k}} c_{k-1} \vee L_i) \right. \\ \left. - (\exp(-a_{i,k}) + c_k \wedge R_i) \exp(-e^{a_{i,k}} c_k \wedge R_i) \right\} \frac{\exp(e^{a_{i,k}} c_{k-1} - \sum_{j=1}^{k-1} e^{a_{i,j}} (c_j - c_{j-1}))}{S(L_i | Z_i, \boldsymbol{\theta}) - S(R_i | Z_i, \boldsymbol{\theta})},$$

such that

$$\frac{\partial L_{i,1}^{\text{obs}}(\boldsymbol{\theta})}{\partial a_k} = C_{i,k}(\boldsymbol{\theta}) - e^{a_{i,k}} \left(D_{i,k}(\boldsymbol{\theta}) - c_{k-1} C_{i,k}(\boldsymbol{\theta}) \right) - e^{a_{i,k}} (c_k - c_{k-1}) \sum_{l=k+1}^K C_{i,l}(\boldsymbol{\theta}),$$

$$\frac{\partial L_{i,1}^{\text{obs}}(\boldsymbol{\theta})}{\partial \beta} = Z_i \left\{ C_{i,k}(\boldsymbol{\theta}) - C_{i,k}(\boldsymbol{\theta}) \sum_{j=1}^{k-1} e^{a_{i,j}} (c_j - c_{j-1}) - e^{a_{i,k}} \left(D_{i,k}(\boldsymbol{\theta}) - c_{k-1} C_{i,k}(\boldsymbol{\theta}) \right) \right\}.$$

For the exact observations we have

$$\frac{\partial L_{i,2}^{\text{obs}}(\boldsymbol{\theta})}{\partial a_k} = O_{i,k} - \exp(a_k + \beta Z_i) R_{i,k},$$

$$\frac{\partial L_{i,2}^{\text{obs}}(\boldsymbol{\theta})}{\partial \beta} = Z_i \sum_{l=1}^K \left\{ O_{i,l} - \exp(a_l + \beta Z_i) R_{i,l} \right\}.$$

For the Hessian matrix $\partial^2 \log(L^{\text{obs}}(\boldsymbol{\theta}))/\partial \boldsymbol{\theta}^2$, we first compute

$$\frac{\partial S(c_{k-1} \vee L_i | Z_i, \boldsymbol{\theta})}{\partial a_k} = -(L_i I_k(L_i) + c_k I(L_i > c_k)) e^{a_{i,k}} S(L_i | Z_i, \boldsymbol{\theta}),$$

$$\frac{\partial S(c_{k-1} \vee L_i | Z_i, \boldsymbol{\theta})}{\partial \beta} = -Z_i \sum_{l=1}^K (c_l \wedge c_{k-1} \vee L_i - c_{l-1}) I(c_{l-1} \leq c_{k-1} \vee L_i) e^{a_{i,k}} S(c_{k-1} \vee L_i | Z_i, \boldsymbol{\theta}),$$

$$\frac{\partial S(c_k \wedge R_i | Z_i, \boldsymbol{\theta})}{\partial a_k} = -(c_k \wedge R_i - c_{k-1}) e^{a_{i,k}} S(c_k \wedge R_i | Z_i, \boldsymbol{\theta}) I(R_i \geq c_{k-1}),$$

$$\frac{\partial S(c_k \wedge R_i | Z_i, \boldsymbol{\theta})}{\partial \beta} = -Z_i \sum_{l=1}^K (c_l \wedge c_k \wedge R_i - c_{l-1}) I(c_{l-1} \leq c_k \wedge R_i) e^{a_{i,k}} S(c_k \wedge R_i | Z_i, \boldsymbol{\theta}),$$

$$\frac{\partial S(L_i | Z_i, \boldsymbol{\theta})}{\partial a_k} = -(c_k \wedge L_i - c_{k-1}) e^{a_{i,k}} S(L_i | Z_i, \boldsymbol{\theta}) I(L_i \geq c_{k-1}),$$

$$\frac{\partial S(L_i | Z_i, \boldsymbol{\theta})}{\partial \beta} = -Z_i \sum_{l=1}^K (c_l \wedge L_i - c_{l-1}) e^{a_{i,l}} S(L_i | Z_i, \boldsymbol{\theta}) I(L_i \geq c_{l-1}),$$

$$\frac{\partial S(R_i | Z_i, \boldsymbol{\theta})}{\partial a_k} = -(c_k \wedge R_i - c_{k-1}) e^{a_{i,k}} S(R_i | Z_i, \boldsymbol{\theta}) I(R_i \geq c_{k-1}),$$

$$\frac{\partial S(R_i | Z_i, \boldsymbol{\theta})}{\partial \beta} = -Z_i \sum_{l=1}^K (c_l \wedge R_i - c_{l-1}) e^{a_{i,l}} S(R_i | Z_i, \boldsymbol{\theta}) I(R_i \geq c_{l-1}),$$

such that calculation of the partial derivatives of $C_{i,k}(\boldsymbol{\theta})$ are calculated from the formulas

$$\begin{aligned}\frac{\partial C_{i,k}(\boldsymbol{\theta})}{\partial a_k} &= \frac{\partial S(c_{k-1} \vee L_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k - \partial S(c_k \wedge R_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})} \\ &\quad - C_{i,k}(\boldsymbol{\theta}) \frac{\partial S(L_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k - \partial S(R_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})}, \\ \frac{\partial C_{i,k}(\boldsymbol{\theta})}{\partial \beta} &= \frac{\partial S(c_{k-1} \vee L_i \mid Z_i, \boldsymbol{\theta}) / \partial \beta - \partial S(c_k \wedge R_i \mid Z_i, \boldsymbol{\theta}) / \partial \beta}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})} \\ &\quad - C_{i,k}(\boldsymbol{\theta}) \frac{\partial S(L_i \mid Z_i, \boldsymbol{\theta}) / \partial \beta - \partial S(R_i \mid Z_i, \boldsymbol{\theta}) / \partial \beta}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})}.\end{aligned}$$

Then, we can show that

$$\begin{aligned}\frac{\partial}{\partial a_k} \sum_{l=k+1}^K C_{i,l}(\boldsymbol{\theta}) &= \frac{(c_k \vee L_i - c_{k-1}) e^{a_{i,k}} \sum_{l=k}^K S(c_l \vee L_i \mid Z_i, \boldsymbol{\theta})}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})} \\ &\quad - \frac{(c_k \wedge R_i - c_{k-1}) e^{a_{i,k}} I(R_i \geq c_{k-1}) \sum_{l=k+1}^K S(c_l \vee R_i \mid Z_i, \boldsymbol{\theta})}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})} \\ &\quad - \sum_{l=k+1}^K C_{i,l}(\boldsymbol{\theta}) \frac{\partial S(L_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k - \partial S(R_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})}.\end{aligned}$$

We now introduce:

$$\begin{aligned}E_{i,k} &= \exp(-a_{i,k} - e^{a_{i,k}} c_{k-1} \vee L_i) + (\exp(-a_{i,k}) + c_{k-1} \vee L_i) (\exp(a_{i,k} - e^{a_{i,k}} c_{k-1} \vee L_i) c_{k-1} \vee L_i) \\ &\quad + \exp(-a_{i,k} - e^{a_{i,k}} c_{k-1} \vee L_i) + (\exp(-a_{i,k}) + c_k \wedge R_i) (\exp(a_{i,k} - e^{a_{i,k}} c_k \wedge R_i) c_k \vee R_i),\end{aligned}$$

such that

$$\begin{aligned}\frac{\partial D_{i,k}(\boldsymbol{\theta})}{\partial a_k} &= - \frac{E_{i,k} \exp(e^{a_{i,k}} c_{k-1} - \sum_{j=1}^{k-1} e^{a_{i,j}} (c_j - c_{j-1})) J_{k,i}}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})} + D_{i,k}(\boldsymbol{\theta}) e^{a_{i,k}} c_{k-1} J_{k,i} \\ &\quad - D_{i,k}(\boldsymbol{\theta}) \frac{\partial S(L_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k - \partial S(R_i \mid Z_i, \boldsymbol{\theta}) / \partial a_k}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})} J_{k,i}, \\ \frac{\partial D_{i,k}(\boldsymbol{\theta})}{\partial \beta} &= - Z_i \frac{E_{i,k} \exp(e^{a_{i,k}} c_{k-1} - \sum_{j=1}^{k-1} e^{a_{i,j}} (c_j - c_{j-1})) J_{k,i}}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})} \\ &\quad + Z_i D_{i,k}(\boldsymbol{\theta}) (e^{a_{i,k}} c_{k-1} - \sum_{j=1}^{k-1} e^{a_{i,j}} (c_j - c_{j-1})) J_{k,i} \\ &\quad - D_{i,k}(\boldsymbol{\theta}) J_{k,i} \frac{\partial S(L_i \mid Z_i, \boldsymbol{\theta}) / \partial \beta - \partial S(R_i \mid Z_i, \boldsymbol{\theta}) / \partial \beta}{S(L_i \mid Z_i, \boldsymbol{\theta}) - S(R_i \mid Z_i, \boldsymbol{\theta})}.\end{aligned}$$

Finally, we have

$$\begin{aligned}
\frac{\partial^2 L_1^{\text{obs}}(\boldsymbol{\theta})}{\partial a_k^2} &= \frac{\partial C_{i,k}(\boldsymbol{\theta})}{\partial a_k} - e^{a_i,k} \left(D_{i,k}(\boldsymbol{\theta}) - c_{k-1} C_{i,k}(\boldsymbol{\theta}) + \frac{\partial D_{i,k}(\boldsymbol{\theta})}{\partial a_k} - c_{k-1} \frac{\partial C_{i,k}(\boldsymbol{\theta})}{\partial a_k} \right) \\
&\quad - e^{a_i,k} (c_k - c_{k-1}) \left(\sum_{l=k+1}^K C_{i,l}(\boldsymbol{\theta}) + \frac{\partial}{\partial a_k} \sum_{l=k+1}^K C_{i,l}(\boldsymbol{\theta}) \right), \\
\frac{\partial^2 L_1^{\text{obs}}(\boldsymbol{\theta})}{\partial a_k \partial \beta} &= Z_i \left\{ \frac{\partial C_{i,k}(\boldsymbol{\theta})}{\partial a_k} - \frac{\partial C_{i,k}(\boldsymbol{\theta})}{\partial a_k} \sum_{j=1}^{k-1} e^{a_i,j} (c_j - c_{j-1}) \right. \\
&\quad \left. - e^{a_i,k} \left(D_{i,k}(\boldsymbol{\theta}) - c_{k-1} C_{i,k}(\boldsymbol{\theta}) + \frac{\partial D_{i,k}(\boldsymbol{\theta})}{\partial a_k} - c_{k-1} \frac{\partial C_{i,k}(\boldsymbol{\theta})}{\partial a_k} \right) \right\}, \\
\frac{\partial^2 L_1^{\text{obs}}(\boldsymbol{\theta})}{\partial \beta^2} &= Z_i \left\{ \frac{\partial C_{i,k}(\boldsymbol{\theta})^t}{\partial \beta} - \frac{\partial C_{i,k}(\boldsymbol{\theta})^t}{\partial \beta} \sum_{j=1}^{k-1} e^{a_i,j} (c_j - c_{j-1}) \right. \\
&\quad \left. - e^{a_i,k} \left(Z_i^t D_{i,k}(\boldsymbol{\theta}) - c_{k-1} Z_i^t C_{i,k}(\boldsymbol{\theta}) + \frac{\partial D_{i,k}(\boldsymbol{\theta})^t}{\partial \beta} - c_{k-1} \frac{\partial C_{i,k}(\boldsymbol{\theta})^t}{\partial \beta} \right) \right\},
\end{aligned}$$

and for the exact observations

$$\begin{aligned}
\frac{\partial^2 L_2^{\text{obs}}(\boldsymbol{\theta})}{\partial a_k^2} &= -\exp(a_k + \beta Z_i) R_{i,k}, \\
\frac{\partial^2 L_2^{\text{obs}}(\boldsymbol{\theta})}{\partial a_k \partial \beta} &= -Z_i \exp(a_k + \beta Z_i) R_{i,k}, \\
\frac{\partial^2 L_2^{\text{obs}}(\boldsymbol{\theta})}{\partial \beta^2} &= -Z_i Z_i^t \sum_{l=1}^K \left\{ \exp(a_l + \beta Z_i) R_{i,l} \right\}.
\end{aligned}$$

References

- [1] Bruce W Turnbull. The empirical distribution function with arbitrarily grouped, censored and truncated data. *Journal of the Royal Statistical Society. Series B (Methodological)*, pages 290–295, 1976.
- [2] Piet Groeneboom and Jon A Wellner. *Information bounds and nonparametric maximum likelihood estimation*, volume 19. Springer Science and Business Media, 1992.
- [3] Geurt Jongbloed. The iterative convex minorant algorithm for nonparametric estimation. *Journal of Computational and Graphical Statistics*, 7(3):310–321, 1998.
- [4] Jian Huang and Jon A Wellner. Efficient estimation for the proportional hazards model with “case 2” interval censoring. Technical Report 290, Department of Statistics, University of Washington, Seattle, 1995.
- [5] Audrey Boruvka and Richard J Cook. A cox-aalen model for interval-censored data. *Scandinavian Journal of Statistics*, 42(2):414–426, 2015.
- [6] JK Lindsey. A study of interval censoring in parametric regression models. *Lifetime data analysis*, 4(4):329–354, 1998.
- [7] Jianguo Sun. *The statistical analysis of interval-censored failure time data*. Springer Science and Business Media, 2007.

- [8] Rebecca A Betensky, Jane C Lindsey, Louise M Ryan, and MP Wand. A local likelihood proportional hazards model for interval censored data. *Statistics in Medicine*, 21(2):263–275, 2002.
- [9] Lianming Wang, Christopher S McMahan, Michael G Hudgens, and Zaina P Qureshi. A flexible, computationally efficient method for fitting the proportional hazards model to interval-censored data. *Biometrics*, 72(1):222–231, 2016.
- [10] Arthur P Dempster, Nan M Laird, and Donald B Rubin. Maximum likelihood from incomplete data via the em algorithm. *Journal of the royal statistical society. Series B (methodological)*, pages 1–38, 1977.
- [11] Bendix Carstensen. Regression models for interval censored survival data: application to hiv infection in danish homosexual men. *Statistics in Medicine*, 15(20):2177–2189, 1996.
- [12] Florian Frommlet and Grégory Nuel. An adaptive ridge procedure for l0 regularization. *PLoS ONE*, 11(2), 2016.
- [13] Ralph CA Rippe, Jacqueline J Meulman, and Paul HC Eilers. Visualization of genomic changes by segmented smoothing using an l0 penalty. *PloS one*, 7(6), 2012.
- [14] Olivier Bouaziz and Grégory Nuel. L0 regularization for the estimation of piecewise constant hazard rates in survival analysis. *Applied Mathematics*, 8(3), 2017.
- [15] Judy P Sy and Jeremy MG Taylor. Estimation in a cox proportional hazards cure model. *Biometrics*, 56(1):227–236, 2000.
- [16] Yingwei Peng and Keith BG Dear. A nonparametric mixture model for cure rate estimation. *Biometrics*, 56(1):237–243, 2000.
- [17] Tao Hu and Liming Xiang. Partially linear transformation cure models for interval-censored data. *Computational Statistics & Data Analysis*, 93:257–269, 2016.
- [18] Hao Liu and Yu Shen. A semiparametric regression cure model for interval-censored data. *Journal of the American Statistical Association*, 104(487):1168–1178, 2009.
- [19] Zhigang Zhang, Liuquan Sun, Xingqiu Zhao, and Jianguo Sun. Regression analysis of interval-censored failure time data with linear transformation models. *Canadian Journal of Statistics*, 33(1):61–70, 2005.
- [20] O. O. Aalen, Ø. Borgan, and H. K. Gjessing. *Survival and Event History Analysis*. Statistics for Biology and Health. Springer, 2008.
- [21] Ravi Varadhan and Christophe Roland. Simple and globally convergent methods for accelerating the convergence of any em algorithm. *Scandinavian Journal of Statistics*, 35(2):335–353, 2008.
- [22] Mai Zhou. *Empirical likelihood method in survival analysis*. Chapman and Hall/CRC, 2015.
- [23] JO Andreasen, MK Borum, HL Jacobsen, and FM Andreasen. Replantation of 400 avulsed permanent incisors. 1. diagnosis of healing complications. *Dental Traumatology*, 11(2):51–58, 1995.
- [24] JO Andreasen, M Kit Borum, HL Jacobsen, and FM Andreasen. Replantation of 400 avulsed permanent incisors. 4. factors related to periodontal ligament healing. *Dental Traumatology*, 11(2):76–89, 1995.

- [25] Terry M. Therneau and Patricia M. Grambsch. *Modeling survival data: extending the Cox model*. Statistics for Biology and Health. Springer-Verlag, New York, 2000.
- [26] Simon Bussy, Agathe Guilloux, Stéphane Gaïffas, and Anne-Sophie Jannot. C-mix: A high-dimensional mixture model for censored durations, with applications to genetic data. *Statistical methods in medical research*, 2017.