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SMOOTH ESTIMATION OF SURVIVAL FUNCTIONS AND HAZARD RATIOS FROM INTERVAL-CENSORED DATA USING BAYESIAN PENALIZED B-SPLINES

ÇETINYÜREK-YAVUZ, A. and Ph. LAMBERT

Smooth estimation of survival functions and hazard ratios from interval-censored data using Bayesian penalized B-splines

Aysun Çetinyürek Yavuz
Institut de Mathematique, Service de Statistique, Université de Liège
Philippe Lambert
Institut des Sciences Humaines et Sociales, Université de Liège
Institut de Statistique , Université catholique de Louvain

Abstract

We discuss the use of Bayesian P-spline and of the composite link model to estimate survival functions and hazard-ratios from interval-censored data. If one further assumes proportionality of the hazards, the proposed strategy provides a smoothed estimate of the baseline hazard along with estimates of global covariate effects. The frequentist properties of our Bayesian estimators are assessed by an extensive simulation study. We further illustrate the methodology by three examples showing that the proportionality of the hazards might also be found inappropriate from interval-censored data.

keywords: interval-censored, Bayesian, P-spline, proportional hazards, composite link model

1 Introduction

There has been increasing interest in statistical analysis of interval-censored time-to-event data. Examples of interval-censored time-to-event data naturally arise in diverse fields, such as medicine, demography, economics, epidemiology, etc. In medicine, this type of data is quite usual for clinical trials or longitudinal studies especially in practical settings of AIDS and cancer research where the individuals have prescheduled visits. Data are collected at every visit: hence, when a change of state is diagnosed, the event time is often only known to have happened since the last visit. Then, time-to-event data takes the form of an interval (L, R) of irregular length where L represents the time of the last negative test result and R represents the time of the first positive test result. Irregular intervals arise when e.g. patients may miss or delay some of the visits.

Interval-censored data is a natural generalization of right censored time-to-event data. For right censored data, extensive number of statistical techniques are available to tackle most research questions under a variety of assumptions. However, for interval-censored data less well developed procedures are available, and the basic strategies such as mid-point imputation lead to invalid inferences. Lack of statistical software packages for this type of censoring has driven many researchers to use imputation techniques, especially right-point or mid-point imputation.

In imputation approach, it is often assumed that the event occurred at the middle of the interval, resulting in biased estimates. As shown by Law and Brookmeyer [27], the statistical properties of the midpoint imputation depend strongly on the width of the interval between visits and the shape of the time to event density. The authors assessed the performance of midpoint imputation to estimate the regression parameter in a proportional hazards model: it was shown that biased estimates may be observed if the intervals are wide. In addition, midpoint imputation wrongly assumes that failure times are known exactly: this leads to underestimated standard errors [17].

Alternatively, one could assume a parametric form for the time-to-event density and fit a regression model to the available interval-censored failure times using standard statistical softwares (e.g. Proc LIFEREG in SAS). When the underlying density has a simple shape, the parametric method can work quite well, but when it is skewed or multimodal, or both, a lot of effort is needed to find the right model. A nonparametric model will be more attractive then.

The first nonparametric method for estimating a survival function from interval-censored data was suggested by Peto [29]. Afterwards, Turnbull [35] derived the same estimator using a different approach. He proposed a 'self-consistency method' for univariate interval-censored data, but the solution was not always unique [38]. Kooperberg and Stone [22] developed logspline density estimation for univariate data (right-, left-or interval-censored) using cubic B-spline basis. Hansen and Kooperberg [14] investigated the problem of logspline density estimation in a Bayesian context for non-censored data. The authors constructed the logarithm of a density as a sum of natural cubic regression splines (with number of knots and their location to be estimated) and then introduced specialized priors.

The most popular regression model for time-to-event data is the Cox proportional hazards (PH) model [6] for assessing the effect of covariates on a response. If T denotes the observed time-to-event, then the Cox PH model assumes that:

$$h(t|\boldsymbol{x}) = h_0(t)\exp(\boldsymbol{x'\beta}), \tag{1}$$

where $h_0(t)$ is the baseline hazard at time t and $h(t|\boldsymbol{x})$ conditional hazard at time t given covariates $\mathbf{x}$ and regression coefficients $\boldsymbol{\beta}$. The primary interest is usually in the estimation of the regression coefficients $\boldsymbol{\beta}$. However, the shape of the baseline hazard function might be of specific interest (see e.g. [25, 32, 39]).

Several authors discussed the use of Cox PH model for left- or right-censored time-to-event data. However, Finkelstein [9] was the first to discuss a PH model for interval-censored time-to-event data, proposing a generalization of log-rank test for comparison of survival curves. Goetghebeur and Ryan [12] proposed to use of an approximate likelihood by employing an EM algorithm to fit a semiparametric Cox PH model for interval-censored data. Then in 2002, Betensky *et al.* discussed the local likelihood methods to fit a PH model for interval-censored data where an interpretable smoothed baseline hazard function was estimated along with estimates of log hazard ratio[3]. A recent approach proposed for regression analysis of interval-censored data considered a reparametrization of the log hazard function through a mixed model approach [5]. The authors obtained a smooth estimate of the hazard function by maximizing the penalized likelihood. Komarek *et al.* [18] proposed a methodology that implemented a maximum likelihood-based approach for an accelerated failure time model. Smoothed estimates of the baseline density and of the regression coefficients were obtained by Komarek *et al.* [18] by assuming a mixture of normal distributions for the conditional distributions in accelerated failure time model. More recently Zhang and Davidian [40] proposed a general regression framework for arbitrarily-censored data. It includes as special cases, the Cox PH and accelerated failure time models. They provided an attractive approximation to basically any plausible time-to-event density by assuming a broad class of densities which elements may be approximated by the semi-nonparametric density estimator [10].

Following Eilers and Marx [8] and Lambert and Eilers [25, 26] in a Bayesian framework, we propose to model the log density as a linear combination of B-splines associated to a large number of equidistant knots. This flexibility is counterbalanced by a suitable smoothness prior on the spline coefficients. The composite link model (CLM; [36]) was successfully used by Lambert and Eilers [26] to estimate density from grouped (histogram) data. Here we extend their methodology to deal with arbitrarily interval-censored data in a Cox PH model framework.

The organization of the rest of this paper is as follows. In the next section, after having introduced some notation we present our strategy for estimating the time-to-event density from interval-censored data. The building blocks are penalized B-splines and the composite link model [36]. In the third section, we show how this can be extended to the Cox PH model. Section 4 is devoted to the Bayesian variant of the model allowing the uncertainties to be quantified in the model parameters and derived quantities. Markov chain Monte Carlo (MCMC) is used to explore the joint posterior. In the fifth section, the results of a large simulation study are reported. Illustrations are proposed in Section 6. We conclude the paper by a discussion.

2 Density Estimation for Interval-Censored Data

Denote by T_j the (continuous) time until the event of interest occurs for unit j ($j = 1, ..., N$). Assuming independence and a common distribution for $T_1, \ldots T_N$, let f be the probability density and F the corresponding cumulative distribution function for T_j. Time T_j is not observed exactly, but instead only known to lie in an interval (L_j, R_j) in the support (a, b). Based on interval censored data $\{(L_j, R_j) : j = 1, \ldots, N\}$, we want to obtain an estimate of f on $(a, t_{cens}) \subset (a, b)$ where $t_{cens} \leq b$ and $\zeta = P(T_j > t_{cens})$. Following Lambert and Eilers [26], we partition (a, t_{cens}) into many (100 or more grid points, say) small intervals $I_i = (a_{i-1}, a_i)$ of equal width Δ with midpoints $u_i = a_{i-1} + 0.5\Delta$ ($i = 1, ..., I$). Then, the quantities of interest are $\pi_i = \int_{I_i} f(t)dt \approx f(u_i)\Delta_i$ where π_i denotes the probability to observe T_j in I_i. The relationship between the partition and the observed intervals is provided by an n by I matrix $C = [c_{ji}]$, where $c_{ji} = 1$ if $I_i \subset (L_j, R_j)$ and 0 otherwise. Let $d_j = 1$ if $R_j > t_{cens}$ and 0 otherwise. Then, the probability γ_j to observe (L_j, R_j) for unit j could be expressed as

$$\gamma_j = \sum_i c_{ji} \times \pi_i + d_j \times (1 - \zeta). \tag{2}$$

In Figure 1, the construction of the C matrix is illustrated for a simulated data set assuming that the study ended at time t_{cens}=80 (see Section 5 for further details). Only ten 'small' bins of width 8 were considered for visual purposes (while around 100 of them were taken in the example below).

Hence, the likelihood is expressed as proportional to:

$$l = \prod_{j=1}^{N} P[L_j < T_j < R_j] = \prod_j \gamma_j.$$

The estimation of the π_i's is an ill-conditioned problem since the available data only refer to the interval probabilities γ_j ($j = 1, \ldots N$). Therefore we require the π_i's to change smoothly over time. Using the approach of Eilers and Marx [8], the π_i's are modeled using penalized B-splines. Some familiarity with penalized B-splines is assumed from the reader as only a brief summary is given here, see [8] for more details. A B-spline of degree q consists of $q + 1$ polynomial pieces of degree q connected in a smooth way at q inner knots. It is positive on the interval spanned by $q + 2$ consecutive knots and zero elsewhere. The solid curve in Figure 2 (left panel) was

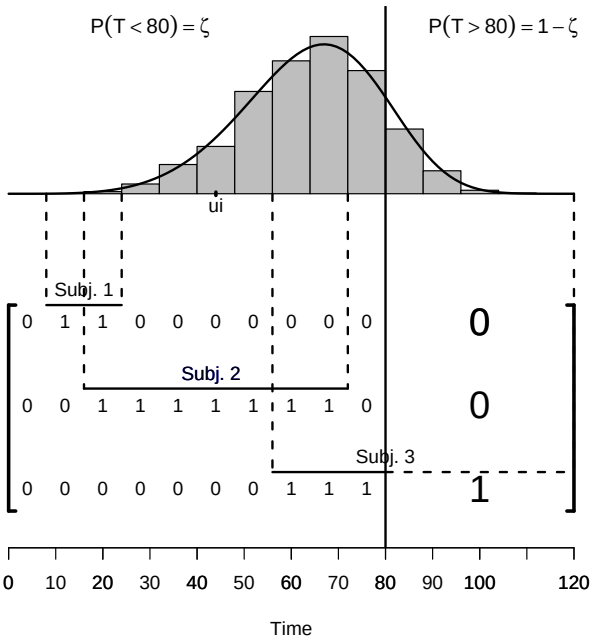


Figure 1: Illustrative data: Construction of C matrix for interval censored data on [0,120] where study ends at time 80 (t_{cens}=80) and small bins have width of 8

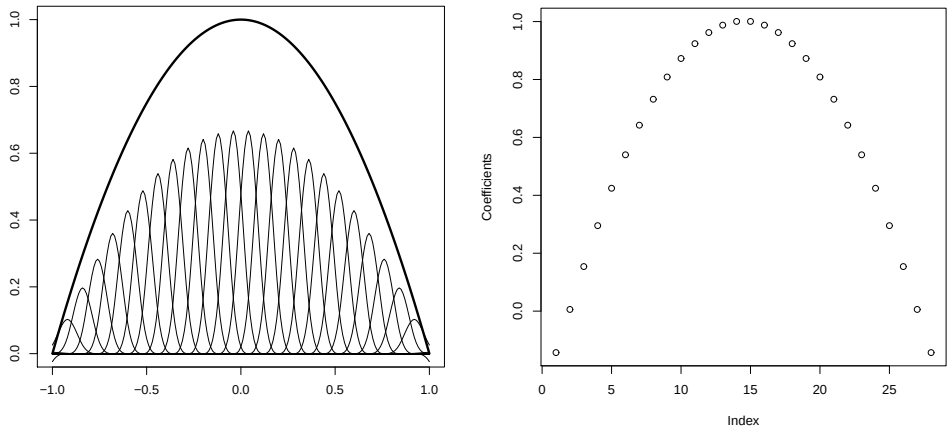
approximated using a linear combination of cubic B-splines corresponding to a large number of equidistant knots on [-1,1]. The bell shape curves on the same graph are the B-splines of the basis multiplied by an estimate (see below) of their multiplying coefficient. Thanks to the large number of knots the target curve and its estimate cannot be distinguished. From the right panel of Figure 2, one can notice that the B-spline coefficients depict the same shape as the target curve. This suggests that desired properties (such as monotonicity, concavity, etc.) for the fitted curve can be ensured by enforcing these properties on the spline coefficients.

Consider now the B-spline basis $\{b_k(., q) : k = 1, ..., K\}$ of degree q associated to a rich grid (say 20) of equidistant knots on (a, t_{cens}). Let ζ denote the probability to observe the event before t_{cens}. Given the partition of (a, t_{cens}) into I intervals I_i $(i = 1, ..., I)$ of equal width (see above), the probability π_i that $T \in I_i$ can be modeled using polytomous regression as:

$$\pi_i = \zeta \times \frac{e^{\eta_i}}{e^{\eta_1} + e^{\eta_2} + ... + e^{\eta_I}},$$

where $\eta_i = \sum_k \phi_k b_{ik}$ and u_i is the midpoint of I_i (i=1, ..., I). An identifiability constraint is imposed on the spline coefficients, ϕ_k, such that $\sum_k \phi_k = 0$ since $\pi_i(\phi) = \pi_i(\phi + c)$ for any constant c.

In order to counterbalance the flexibility of the generous B-spline basis, we apply a discrete roughness penalty on (rth order) changes in the B-spline coefficients [8]. The roughness penalty for the B-spline coefficients is based on squared finite (rth order) differences of the coefficients of adjacent B-splines. For example, a second-order (r=2) difference penalty is given by $\sum_k (\phi_k - 2\phi_{k-1} + \phi_{k-2})^2 = \boldsymbol{\phi' D' D \phi}$ where:



(a) (b)

Figure 2: (a): Curve approximated by linear combination of B-splines. (b): Estimated spline coefficients.

$$\mathbf{D} = \begin{pmatrix} 1 & -2 & 1 & 0 & \dots & 0 \\ 0 & 1 & -2 & 1 & \dots & 0 \\ \vdots & \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & 0 & \dots & 1 & -2 & 1 \end{pmatrix}.$$

Apart from the penalty, the model for $\boldsymbol{\gamma}$ in Equation (2) can be seen as a composite link model [36] with composing matrix $[C, \boldsymbol{d}]$. It was used in a Bayesian framework by Lambert and Eilers [26] to estimate a density from grouped (histogram) data.

3 Extension to the Cox Proportional Hazards Model

We have specified a model for the density when the available data are interval-censored. Before examining Bayesian inference in Section 4, here is an an extension to the Cox PH model. Denote the smooth model for the density f_0 (see Section 2) for reference values of the covariates ($\boldsymbol{x} = 0$) by $\widetilde{f_0}$. By definition, it is clear that

$$S_0(t) = Pr(T > t | x = 0) = 1 - F_0(t) = 1 - \int_0^t f_0(s)ds, \tag{3}$$

where $S_0(t)$ denotes the baseline survival function. The density and the survival functions are related to the baseline hazard by:

$$h_0(t) = \frac{f_0(t)}{S_0(t)}. \tag{4}$$

The consecutive expressions for the modeled reference survival and hazard functions, $\widetilde{S_0}(t; \phi, \zeta)$ and $\widetilde{h_0}(t; \phi, \zeta)$, can be derived by substituting $\widetilde{f_0}$ for f_0 in Eqs. (3) and (4).

Under the hypothesis of a Cox PH model, the conditional survival function is:

$$S(T \mid \boldsymbol{X} = \boldsymbol{x}) = Pr(T > t|\boldsymbol{X} = \boldsymbol{x}) = S_0(t)^{\exp(\boldsymbol{x'\beta})}, \tag{5}$$

and conditional hazard function is given by (1). Thus, after substitution by the spline approximation to $S_0(t)$, the likelihood for the Cox PH model for interval censored data is proportional to

$$\ell = \ell(\boldsymbol{\phi}, \boldsymbol{\zeta}, \boldsymbol{\beta}) = \prod_j \widetilde{P}[L_j < T_j < R_j|\boldsymbol{x_j}] = \prod_j [\widetilde{S}(L_j|\boldsymbol{x_j}) - \widetilde{S}(R_j|\boldsymbol{x_j})]. \tag{6}$$

4 Bayesian Model Formulation

Having introduced the Cox PH model based on P-splines in the previous section, let us now specify the prior distributions for the model parameters.

Denote by τ the penalty parameter in a Bayesian framework: the frequentist roughness penalty for B-splines is translated into a prior distribution on finite (rth order) differences of spline coefficients as:

$$(\Delta^r \phi|\tau) \sim N(0, \tau^{-1}).$$

As a result, the joint prior for the B-splines coefficients is given by:

$$p(\boldsymbol{\phi}|\tau) \propto \tau^{K/2} \exp\left\{-\frac{\tau}{2}\boldsymbol{\phi'P\phi}\right\}, \tag{7}$$

where $\boldsymbol{P} = \boldsymbol{D'D} + \epsilon I$ is a full-rank matrix for some small quantity ϵ (say 10^{-6}). It corresponds to a multivariate normal distribution with mean $\mathbf{0}$ and variance-covariance matrix $\boldsymbol{P}^{-1}$. This idea was successfully used in many context (see e.g. [23] - [26]). The inverse variance τ plays the role of the penalty parameter in the penalized likelihood of the frequentist setting. A large variance hyperprior is usually advocated for τ, say a gamma distribution $\mathcal{G}(a{=}1,\ b{=}0.0001)$ with mean a/b and variance a/b^2 [23]. Alternative priors are proposed in [15] and in [34].

We propose to take an improper flat prior for the set of regression parameters β and a uniform prior on (0,1) for $\zeta = P(T \leq t_{cens}|X = 0)$. More conveniently, we shall work with $\xi = \log[\zeta/(1-\zeta)]$. The consequent prior for ξ is thus proportional to

$$\zeta(1-\zeta) = \frac{\exp(\xi)}{(1+\exp(\xi))^2}.$$

In summary, our priors for the Bayesian Cox PH model based on P-splines are:

$$\begin{array}{lcl} \mathrm{p}(\phi|\tau) & \propto & \tau^{K/2} \exp\left\{-\frac{\tau}{2}\phi' P \phi\right\}, \\ p(\tau) & \propto & \tau^{a-1} \exp(-b\tau), \\ p(\xi) & \propto & \frac{\exp(\xi)}{(1+\exp(\xi))^2} \text{ with } \xi = \log\left(\frac{\zeta}{1-\zeta}\right), \\ p(\beta) & \propto & 1. \end{array}$$

Combined with the likelihood, one gets the joint posterior:

$$p\left(\boldsymbol{\phi}, \tau, \xi, \boldsymbol{\beta} \mid data\right) \propto \ell \times \tau^{K/2+a-1} \exp\left\{-\tau\left(\frac{\boldsymbol{\phi'P\phi}}{2} + b\right)\right\} \frac{\exp(\xi)}{(1+\exp(\xi))^2}, \tag{8}$$

where ℓ is a function of $\gamma_j = \sum_{u_i <= t_{cens}} c_{ji} \times \pi_i + d_j \times (1 - \zeta)$ given by Equation (6) and 'data' represents the intervals corresponding to all subjects in the study. The joint posterior will be explored using MCMC (see Section 4.2). Notice that the conditional posterior distribution of the roughness penalty can be identified:

$$(\tau \mid \boldsymbol{\phi}, data) \sim \mathcal{G}\left(\frac{K}{2} + a, \frac{\boldsymbol{\phi'P\phi}}{2} + b\right). \tag{9}$$

4.1 Frequentist Estimation

Before going into the details of MCMC, we shall begin with a frequentist estimation of the time-to-event density when the covariates are ignored ($\boldsymbol{\beta} = 0$). This will be used to define good starting values for the chains. For obtaining an accurate density estimate of time-to-event, we have partitioned the support of T into small bins as described previously in Section 2. Then, we follow an approach similar to [8] and hence we calculate the number of observations in each small bin, namely the pseudo-counts. These pseudo-counts, which are later used to build the density estimate, are calculated from the C matrix of the composite link model defined in Section 2. In this spirit, each element of a row in the C matrix is divided by the sum of the elements in that row. The so-obtained numbers provide the contribution of the concerned unit (e.g. a patient) for each small bin partitioning (a, t_{cens}). Then, the contributions for the i^{th} small bin, I_i, are summed over all individuals and rounded to the nearest integer value y_i in order to get the pseudo-count for that small bin. Remembering that π_i denotes the probability to have an event time in I_i, the likelihood for these pseudo-counts is proportional to $\prod_i^I \pi_i^{y_i}$. Alternatively, using the well known link between the Poisson and the multinomial distributions one can assume that the pseudo-counts, y_i, have a Poisson distribution with mean $\mu_i = \pi_i y_+$ conditional on the total number of observations $y_+ = \sum_i^I y_i$. Using a log-linear model for the mean with a rich B-spline basis (over the time axis, see Section 2) as regressors:

$$\log(\mu_i) = \eta_i = \sum_{k=1}^{K} \phi_k b_{ik},$$

one gets the log likelihood:

$$\mathcal{L}(y, \boldsymbol{\phi}) = \sum_{i=1}^{N} y_i \log(\mu_i) - \sum_{i=1}^{N} \mu_i.$$

The penalized log likelihood function is constructed by subtracting the 2^{nd} order penalty (say) from the Poisson log likelihood $\mathcal{L}(y; \boldsymbol{\phi})$ as

$$\mathcal{L}_p = \mathcal{L}(y; \boldsymbol{\phi}) - \frac{\tau}{2} \boldsymbol{\phi'P\phi},$$

such that

$$\boldsymbol{\phi'D'D\phi} = \sum_k (\phi_k - 2\phi_{k-1} + \phi_{k-2})^2,$$

where $\boldsymbol{P} = \boldsymbol{D'D} + \epsilon I$. The optimization of $\mathcal{L}_p$ requires solving the score equations

$$B^T(y - \mu) = \tau \boldsymbol{P\phi}.$$

These can be solved using iteratively reweighted least squares (IRWLS) with

$$(B^T\tilde{W}B + \tau P)\phi = B^T\tilde{W}(y - \tilde{\mu}) + B^T\tilde{W}B\tilde{\phi},$$

where $\tilde{\phi}$ and $\tilde{\mu}$ are current approximations to the solution, and $\widetilde{W}$ is a diagonal matrix with elements $\mu_i(\widetilde{\phi})$. The variance-covariance matrix for the estimated spline coefficients $\boldsymbol{\phi}$ is, at convergence,

$$\Sigma_0 = (B^T W B + \tau \boldsymbol{P})^{-1}. \tag{10}$$

For a detailed explanation, see [8].

The initial optimal (plausible) value of the penalty parameter τ could be selected using information criteria such as AIC or BIC. In our experience, BIC is preferable to AIC that tends to undersmooth the target curve, this point is also emphasized in [33]. BIC is defined as

$$BIC = dev(y; \boldsymbol{\phi}, \tau) + 2 \times \log(I) \times dim(\boldsymbol{\phi}, \tau). \tag{11}$$

The effective dimension, $dim(\boldsymbol{\phi}, \tau)$, of the P-spline fit is defined as the trace of the smoother matrix,

$$B(B'WB + \tau \boldsymbol{P})^{-1}B'W.$$

4.2 Exploring the Posterior using MCMC

Let $\boldsymbol{\vartheta} = (\boldsymbol{\phi}, \tau, \xi, \boldsymbol{\beta})$ be the vector of parameters of length H where $H = K + p + 2$ and p denotes the number of regression parameters. The samples $\left\{\boldsymbol{\vartheta^{(m)}} : m = 1, ..., M\right\}$ will be drawn from the joint posterior via Markov chain Monte Carlo (MCMC) methods. In our Bayesian model, only the conditional distribution for τ is identified as a known density. Hence, we shall follow a Metropolis within Gibbs strategy to sample from the joint posterior $p(\boldsymbol{\vartheta}|data)$ presented in Eq. (8). The H components of ϑ will be updated sequentially using a *univariate Metropolis* procedure [42].

The algorithm consists of the four main steps for updating the chains of the parameters $\boldsymbol{\vartheta} = (\boldsymbol{\phi}, \tau, \xi, \boldsymbol{\beta})$:

- Draw $\boldsymbol{\phi}^{(m)}$ from $p(\boldsymbol{\phi} \mid \tau^{(m-1)}, \xi^{(m-1)}, \boldsymbol{\beta}^{(m-1)}$,data) by univariate Metropolis steps.
- Generate $\tau^{(m)}$ from $\mathcal{G}\left(K + a, (\boldsymbol{\phi}^{'(m)} P \boldsymbol{\phi}^{(m)})/2 + b\right)$ by Gibbs step.
- Draw $\xi^{(m)}$ from $p(\xi \mid \tau^{(m)}, \boldsymbol{\phi}^{(m)}, \boldsymbol{\beta}^{(m-1)}$,data) by univariate Metropolis step.
- Draw $\boldsymbol{\beta}^{(m)}$ from $p(\boldsymbol{\beta} \mid \tau^{(m)}, \boldsymbol{\phi}^{(m)}, \xi^{(m)}$,data) by univariate Metropolis step.

The initial values of the chain $\boldsymbol{\vartheta^{(0)}} = \left(\phi^{(0)}, \tau^{(0)}, \xi^{(0)}, \beta^{(0)}\right)^T$ are chosen as follows:

- A value for $\boldsymbol{\phi}^{(0)}$ can be obtained using the frequentist procedure in Section 4.1.
- We define $\tau^{(0)}$ as the value of τ on a grid yielding the smallest BIC.
- $\zeta^{(0)}$ is taken as the proportion of pseudo-counts corresponding to small bins located below t_{cens}.
- In accordance with the estimation of the spline coefficients, we start by ignoring possible covariate effects: $\boldsymbol{\beta}^{(0)} = 0$

Starting from $\boldsymbol{\vartheta^{(0)}} = \left(\vartheta_1^{(0)}, \ldots \vartheta_{H-1}^{(0)}\right)^T$, the initial state of the chain, the update of the h^{th} component $(h \neq K + 1)$ at iteration m is as follows:

1. Denote the state of the chain after the update of the $(h-1)^{th}$ component by $\boldsymbol{\theta^{(h-1)}} = \left(\vartheta_1^{(m)}, \ldots, \vartheta_{h-1}^{(m)}, \vartheta_h^{(m-1)}, \vartheta_{h+1}^{(m-1)}, \ldots \vartheta_{H-1}^{(m-1)}\right)^T$. Generate z such that $Z \sim N(0,1)$ and build proposal value $\boldsymbol{\theta^{(h)}} = \left(\vartheta_1^{(m)}, \ldots, \vartheta_h^{(m-1)} + \delta_h z, \ldots, \vartheta_{H-1}^{(m-1)}\right)^T$ for $\boldsymbol{\vartheta}$ where δ_h is a tuning parameter that is selected to achieve a target acceptance rate.
2. Accept the proposal $\theta^{(h)}$ with probability:

$$\alpha\left(\boldsymbol{\theta^{(h)}}, \boldsymbol{\theta^{(h-1)}}\right) = \min\left\{1, \frac{p\left(\boldsymbol{\theta^{(h)}} \mid data\right)}{p\left(\boldsymbol{\theta^{(h-1)}} \mid data\right)}\right\}$$

that is ϑ_h is set to $\vartheta_h^{(m-1)} + \delta_h z$ if accepted and to $\vartheta_{h-1}^{(m-1)}$ otherwise.

The chain is run long enough to achieve convergence, yielding M iterations. We ignore the first few thousand iterations (say n_b) as an appropriate burn-in period. The resulting chains of length $(M - n_b)$ can be seen as a random sample from the joint posterior. Based on these, point estimates and credible regions for the quantities of interest can be calculated.

As pointed out by Lambert [24], we could improve mixing and accelerate the procedure by using the Metropolis algorithm on a reparametrized problem. This can be done using an approximation to the 2^{nd} order dependence structure of the conditional posterior. For this purpose the variance covariance matrix, $\mathbf{\Sigma_0}$, of the penalized maximum likelihood estimator of the spline parameters $\boldsymbol{\phi}$ could be calculated using (10) for a fixed and reasonably chosen value of the roughness penalty parameter τ. Then, the posterior can be reparametrized using φ with $\phi = \phi_0 + L\varphi$ where L denotes the lower triangular matrix obtained from the Cholesky decomposition of $\mathbf{\Sigma_0}$. Then, we use the univariate Metropolis algorithm described before on the reparametrized posterior.

The identifiability constraint for spline coefficients is achieved in the MCMC sampling scheme by appropriately centering the coefficients at every iteration.

4.2.1 Automatic Tuning of the Algorithm

It was recommended that the asymptotic acceptance probability should be tuned to be approximately 0.23 for optimal convergence of Metropolis algorithm in high dimensional spaces increasing to 0.44 in one dimension [11, 31]. This can be achieved by a careful choice of the standard deviation δ_h in the generation of proposals in the preceding univariate Metropolis algorithm [1]. Let δ denote the tuning parameter of interest. The value of δ at iteration $m+1$ can be adjusted using the value at iteration m using

$$\sqrt{\delta_{m+1}} = h\left(\sqrt{\delta_m} + \gamma_m\left(\alpha(\vartheta, \vartheta^{(m-1)}) - \overline{\eta}\right)\right)$$

with $\overline{\eta} = 0.44$ and

$$h(x) = \begin{cases} \epsilon & \text{if } x < \epsilon \\ \text{x} & \text{if } x \in (\epsilon, A) \\ \text{A} & \text{if } x > A \end{cases}$$

where ϵ is a very small number (say 0.0001) and A a large one (say 10000). If the targeted acceptance level is not achieved, these constants should be changed. The series $\{\gamma_m\}$ is a non-increasing sequence of positive real numbers such that $|\gamma_m - \gamma_{m-1}| \leq m^{-1}$. Possible choices for γ_m are $\frac{10}{m}$ or $\frac{1}{m}$. Practically, the MCMC algorithm is run for a few hundred iterations with the δ_m's automatically updated to achieve the targeted acceptance rate. Then, the last value of

δ_m in the so-generated chain can be used in a non-adaptive version of the modified Metropolis algorithm to produce the long chain(s) that will be used for inference.

5 Simulation Study

An extensive simulation study was carried out in order to illustrate the numerical performances of the proposed strategy. In the simulation study we considered a Cox PH model with baseline hazard $h_0(t) = 5t^4/70^5$ and two binary covariates: this is a Weibull distribution with mean 64.3 and standard deviation 14.7. The covariates X_1 and X_2 are balanced with coding as follows: $(X_1 = 0, X_2 = 0)$ for baseline group, $(X_1 = 1, X_2 = 0)$ for the first and $(X_1 = 0, X_2 = 1)$ for the second treatment groups. The corresponding regression coefficients were chosen to be β_1=1.5, $\beta_2 = 2.0$. The results given below are based on 500 replications and the sample size $n = 300$ or 600.

For interval-censored data, the amount of censoring and the width of the intervals greatly affect the performance of the method and thus are considered in the planning of the simulation study. We have studied the accuracy of estimation for varying amounts of right censoring and different widths for the intervals. Five different mean widths namely 6 ($\cong 0.4\sigma$), 10 ($\cong 0.7\sigma$), 15 ($\cong 1.0\sigma$), 19 ($\cong 1.3\sigma$), and 23 ($\cong 1.6\sigma$) combined with four different levels of right censoring namely 10%, 20%, 35% and 50% were considered. Combined with the two possible sample sizes this makes $5 \times 4 \times 2 = 40$ different arrangements.

Our data generation and simulation strategy contain the following steps:

1. First, we generated the observations t_j $(j = 1, ..., N)$ using the above Cox PH model.
2. Secondly, each observation t_j was converted into an interval of width w_j where w_j generated from a Gamma distribution with a mean equal to the targeted mean width (see above) and a variance equal to one fifth of the mean. The interval corresponding to t_j was finally defined as $(L_j, R_j) = (t_j - u_j * w_j, t_j + u_j * w_j)$ where u_j is randomly generated from a uniform distribution on (0, 1).
3. For each simulated dataset, initial values for the spline parameters were obtained using the strategy in Section 4.1.
4. We estimated the parameters of interest using MCMC (see Section 4.2). Considering the frequentist estimates as starting values, we run the chain for M iterations and obtain the posterior estimates after ignoring the first n_b iterations.
5. Steps 1-4 were repeated for all data sets (S=500 times) to obtain the Monte Carlo estimates corresponding the quantities of interest.

We considered the compact interval (0,120) as (an approximation to) the support of the target Weibull distribution. The observed range of the considered distribution, (0, t_{cens}), changing for different amounts of right-censoring was divided into small bins of width 1 ($\cong 0.07\sigma$). We used cubic B-splines associated to 12 equidistant knots on (0, t_{cens}) and a third order penalty. A chain of length M=30000 (including a burn-in period of n_b=15000 runs) was constructed to explore the posterior distribution of the model parameters. The posterior of the spline parameters was reparametrized using Σ_0 (see Section 4.2).

The fitted baseline density $\widehat{f}_s$ for the s^{th} data set corresponds to the MCMC estimate of $\frac{1}{M-n_b}\sum_{m=n_b}^{M}\widetilde{f}^{(m)}$ of the mean of the estimated posterior baseline densities. The baseline survival is obtained using the estimated baseline density in Eq. (3). These quantities can be used to derive a point estimate for the mean, standard deviation and some selected quantiles. Further we report on 5%, 15%, 25%, 35%, 50%, 60%, 75%, 85% and 88% quantiles of the baseline survival function. It should however be noted that for some amounts of right censoring, we cannot get

the estimates for baseline survival functions at some quantiles since the density is not observed beyond t_{cens}. Furthermore, for a given dataset, the point estimates for β's, ζ and τ were calculated from the chain using the mean of the generated sample; $(1-\alpha)\times 100\%$ credible interval can be estimated using the $\alpha/2$ and $(1-\alpha/2)$ sample quantiles of the chain. The proportions of so-defined S credible intervals (one for each dataset) including the true value of the parameter of interest were reported as an estimate of the corresponding coverage.

The frequentist properties of these Bayesian estimators are measured in terms of:

- relative bias (Rbias),
- empirical standard errors (ESE),
- root mean squared error (RMSE).

If β (say) is the parameter of interest, then the relative bias is defined as

$$100\left(\frac{\bar{\tilde{\beta}}-\beta}{\beta}\right)$$

where $\bar{\tilde{\beta}}$ is the mean of the estimates for β over the S data sets, i.e. $\bar{\tilde{\beta}}=\frac{1}{S}\sum_s \tilde{\beta}^{(s)}$. RMSE is estimated by:

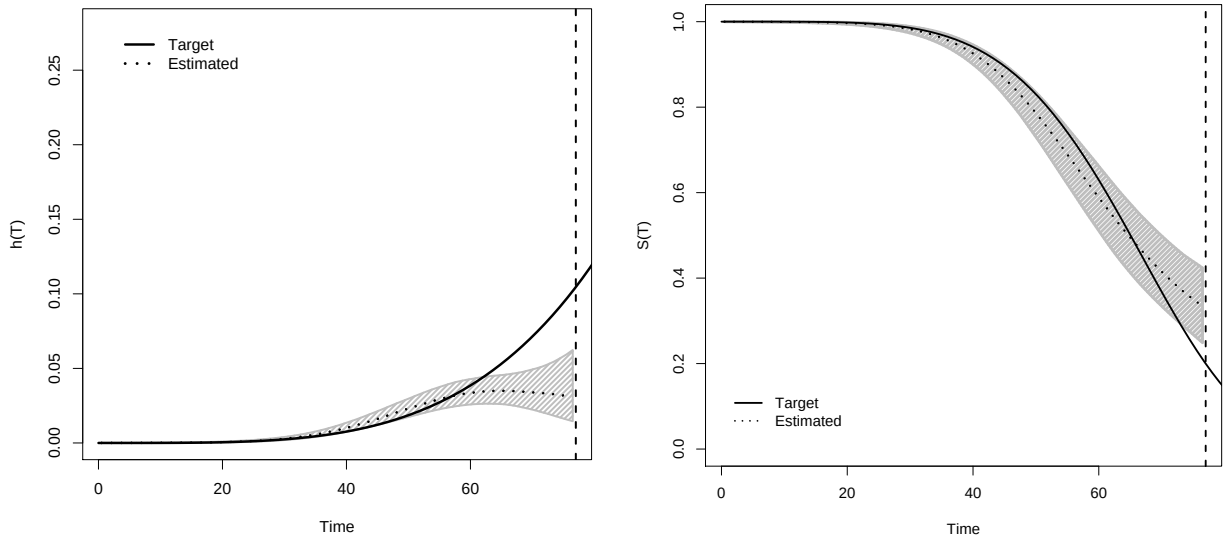
$$\sqrt{\frac{1}{S}\sum(\bar{\tilde{\beta}}-\beta)^2}$$

The results for the regression coefficients are summarized in Table 1 for $n=300$ and in Table 2 for n=600. It is worth highlighting here that regression coefficient estimates have very small bias. The point estimates do not seem to be highly affected from increasing amounts of right-censoring or width of intervals. ESE and RMSE increase as the mean interval width increases; on the other hand, they decrease as sample size increases. Moreover, mean interval width has an effect on the width of 90% credible intervals: as the mean interval width increases, the 90% credible interval gets larger. The width of the credible intervals decreases as sample size increases. Furthermore, the 90% and 80% credible intervals have good coverage probabilities especially for smaller mean interval widths, (0.4σ-1.0σ). The coverage probabilities are very close to nominal values for both sample sizes.

Table 6 and Table 7 presents the Rbias, ESE and RMSE values related to baseline survival function estimate for $n=300$ and 600 respectively. The proposed method generally underestimates the target baseline survival function in the left tail whereas overestimation is observed in the right tail. In the right tail, we can estimate the baseline survival function up to point t_{cens}, but after time t^*,

$$t^* = t_{cens} - (\textit{mean interval width}),$$

we have little information and thus greater uncertainty. From the table, it is easy to notice that for the quantiles less than the value of t^*, the relative bias is very low (0.1% -3%). For the quantiles exceeding t^*, the bias increases with increasing mean interval width. This pattern is appearent for all simulation settings. A marked bias is observed in the right tail of the survival function, especially for larger mean interval widths ($>1.3\sigma$). As a result, the mean interval width seems to have a devastating effect in terms of relative bias only in the quantiles exceeding t^*. On the other hand, the amount of right censoring does not have any impact on the amount of relative bias below that quantity. In that interval, we obtain quite good estimates for the baseline survival function. Furthermore, as sample size increases, ESE and RMSE decrease for the estimated baseline survival function. Besides, the coverages of the 90% credible intervals were presented for the baseline survival function in Table 8 at some selected quantiles of T. The



(a) Estimated Baseline Hazard Function

(b) Estimated Baseline Survival Function

Figure 3: Estimated baseline hazard and survival functions for a simulated data set of sample size n=300 with 20% right censoring and mean interval width of 19 under Cox PH model assumption

coverage probabilities deteriorates for the quantiles exceeding t^* (due to bias), when the mean interval width increases. Elsewhere, the coverage probabilities are close to nominal value.

It should also be emphasized that in case of 0% right censoring, although we considered a support of (0,120) for the baseline density, t_{cens}=98 could be a more realistic alternative since the target density covers an area of 0.995. This explains the increased Rbias and smaller coverage probabilities after t^* (see Tables 3, 9).

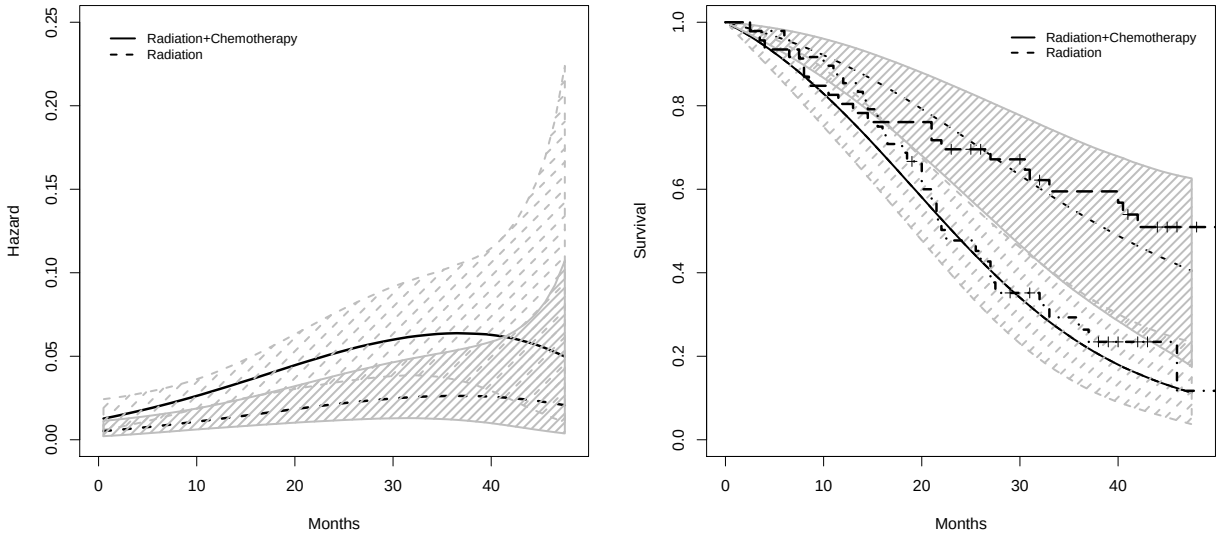
We should point out here that for values of $T > t^*$, the estimated baseline survival function has a better performance than the estimated baseline hazard function. The relative bias for the estimated baseline survival function is less than that of the estimated baseline hazard function. This is illustrated in Figure 3 where we produced plots of baseline survival and baseline hazard functions, with 20% right censoring and mean interval width of 19 (n=300). For the plotted dataset, it is obvious that estimate of the hazard function has substantial bias after 58, larger than for the survival function. This kind of behavior is observed in all simulation settings (see Tables 6,7 and 8). Here the study end time, t_{cens} is taken to be 77 and the mean interval width is 19, and thus we do not have enough information after t^*=58. However, this does not affect the estimates for log hazard ratio as it uses information on the whole time range.

Moreover, Table 4 and Table 5 presents the results for ζ, where ζ=$F(t_{cens})$=$1 - S(t_{cens})$, for sample sizes of n=300 and 600. One can see that ζ is underestimated as a consequence of the greater uncertainty in the right tail. However, it does not affect the performance of the proposed method to estimate log-hazard ratios or the baseline hazard function when T<t^*.

6 Applications

In this section, we discuss three examples from the literature illustrating how the proposed method can be applied to estimate regression coefficients under Cox PH model and to model the baseline survival and baseline hazard curves from interval-censored data. Furthermore, by relaxing the assumption of proportionality, we estimate the baseline survival and hazard functions for each treatment group separately.

For the examples, we performed Bayesian computation using an R code that interface a C function implementing MCMC. We defined a Cox PH model using the above methodology. Then the chain was run for M=60000 iterations with a burn-in period of 40000 along the procedure described in Section 4.2. The required CPU time for the analysis was approximately 75 seconds for the Breast Cosmesis and Hemophiliacs datasets and 150 seconds for the AIDS data set.



(a) Hazard Functions

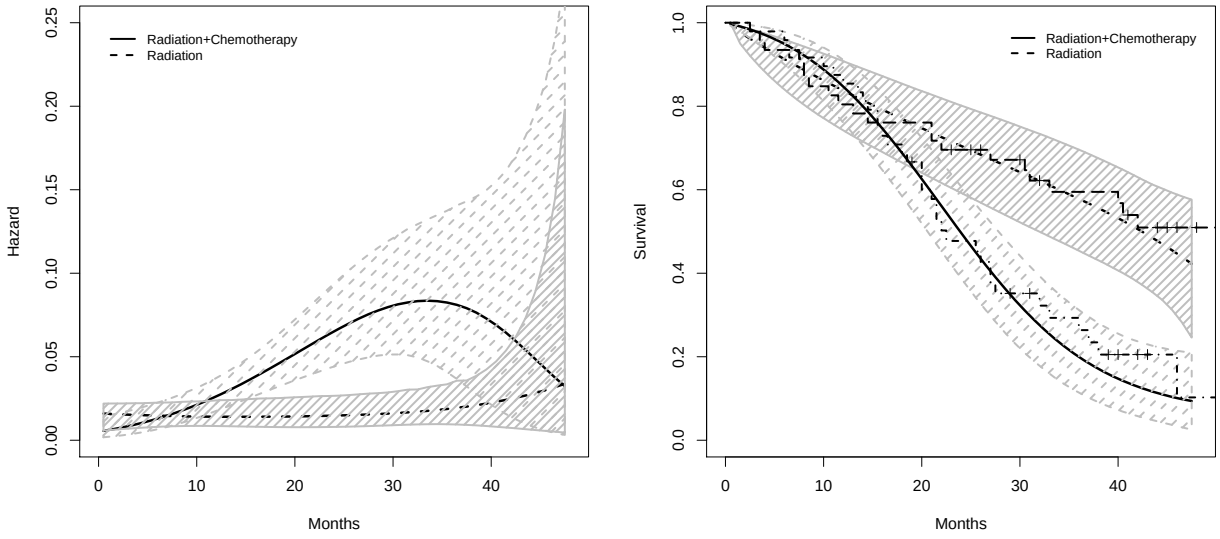
(b) Survival Functions

Figure 4: Breast Cancer dataset: Estimated smooth hazard and survival functions and Kaplan Meier estimates under Cox PH model

6.1 Breast Cancer Data Set

The first example involves reanalysis of a data set that is taken from a retrospective study on early breast cancer patients. The study was carried out to compare the long term cosmetic effects of radiotherapy versus a combined treatment of radiotherapy and adjuvant chemotherapy (defining the baseline group) on women with early breast cancer [41]. Forty six women received radiotherapy alone and 48 women received radiotherapy combined with adjuvant chemotherapy. They were followed during 5 years after treatment on a scheduled basis (on average every 6 months). Breast retraction was found to be highly correlated with cosmetic deterioration [2]. As the patients were only assessed at their clinic visits, deterioration is only known to have occurred

between two successive visits. By the end of the study, it was observed that 56 women had experienced breast retraction (yielding interval-censored data), and 38 had not shown evidence of deterioration (right-censoring) by the end of the study. However, if we investigate the data set in detail, it is obvious that there is only one woman with an interval exceeding 48 months. Therefore, we considered that patient as right-censored assuming that the study ended at month 48 ($=t_{cens}$).



(a) Hazard Functions

(b) Survival Functions

Figure 5: Breast Cancer dataset: Estimated smooth hazard and survival functions without proportionality assumption

As P-spline model, we used a cubic B-spline basis associated to 15 equidistant knots on (0,48) and a third order penalty. Small bins of size 1 were used to divide the support.

The log hazard ratio is estimated to be 0.88 with 90% credible interval (0.39, 1.39) suggesting that chemotheraphy increases the hazard of breast retraction for patients who had previously been treated with radiotheraphy. This is consistent with the estimates found in [3, 5, 12].

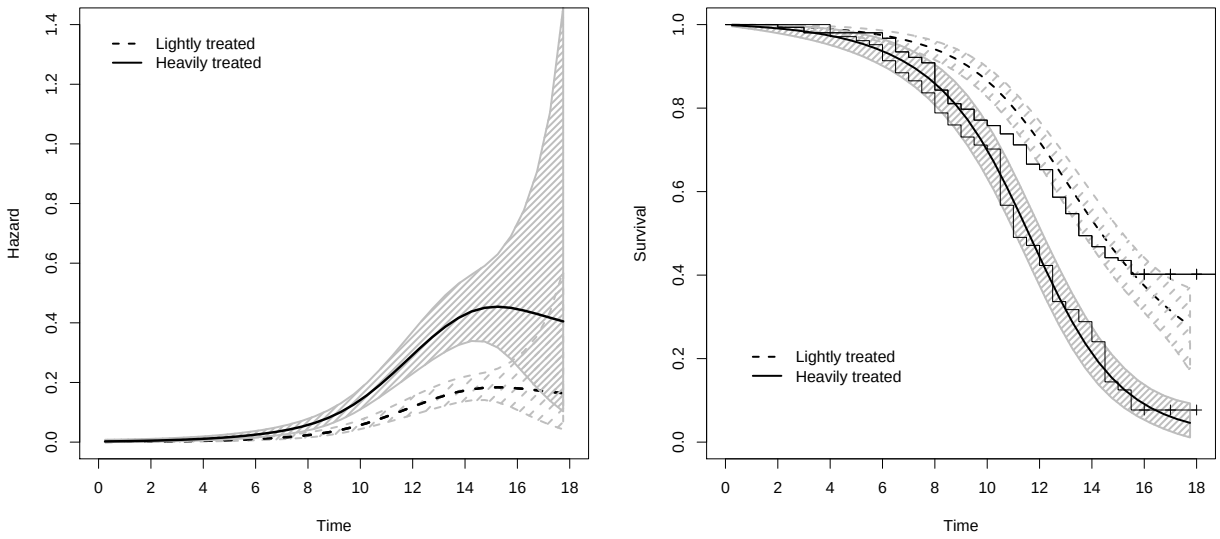
We estimated the probability ζ that the event occurs before t_{cens}=48 in the baseline group as 0.89 ($= 1 - \widetilde{S}_0(t_{cens})$) with 90% credible interval (0.77, 0.96).

It is mentioned in [2] that the cosmetic status declined until 36 months and then stabilized. For that reason we were also interested in estimating the probability to have experienced breast retraction by 36 months. The point estimate and the 90% credible interval were calculated to be 0.23 (0.14,0.34) for the radiation combined with chemotheraphy group, and 0.54 (0.40,0.67) for the radiation group.

In Figure 4, the estimated hazard curves (left panel) and survival curves (right panel) for each treatment group under Cox PH model are presented. Moreover the Kaplan-Meier estimates of the survival curves obtained using midpoint imputation are also displayed in the right panel of Figure 4. Kaplan-Meier estimates and our estimates for survival curves do not follow closely. This is probably due to a violation of the proportionality assumption. When the proportionality

of the hazards assumption is not satisfied, one can estimate the survival curves separately in the two treatment groups, see Figure 5: the two survival curves cross at around month 10 and correctly smooth the Kaplan-Meier estimates.

6.2 Hemophiliacs Data Set



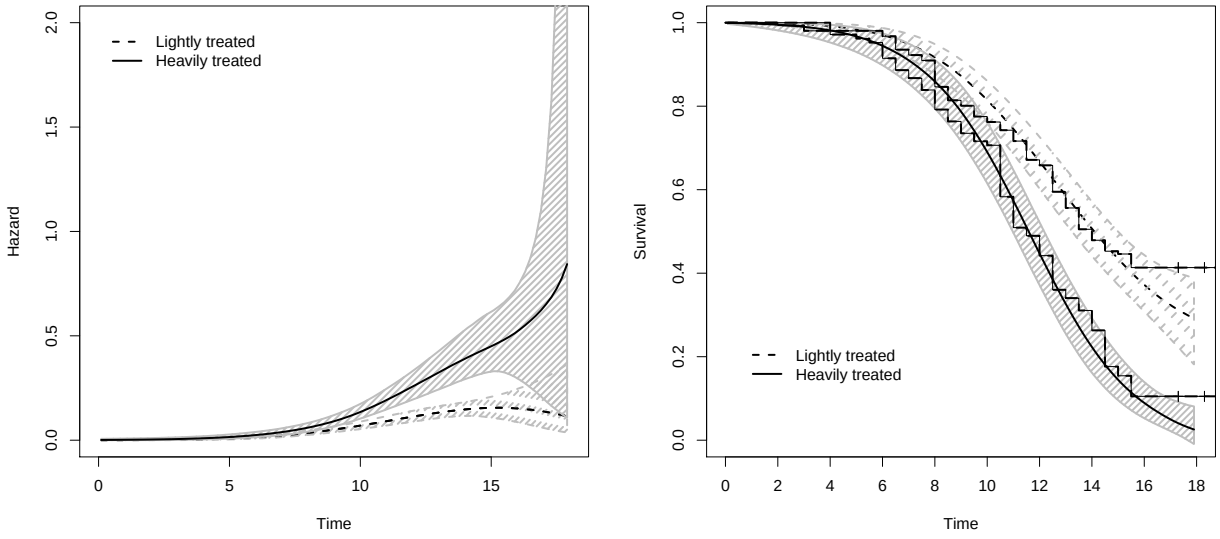
(a) Hazard Functions

(b) Survival Functions

Figure 6: Hemophiliacs data set: Estimated hazard and survival curves for the lightly and heavily treated groups with 90 % credible intervals (dashed and solid shaded, respectively) under Cox PH model

We further illustrate the methodology by an example from [16]. The data set is an extended version of the hemophilia data set published in De Gruttola and Lagakos [7]. The data consists of 257 individuals with Type A or B hemophilia who had been treated with two different treatments at Hôpital Kremlin Bicêtre and Hôpital Coeur des Yvelines in France since 1978. Hemophilia is treated by supplementing low levels of blood factor proteins with healthy replacement blood factors. Of 257 individuals, 153 received blood factor less than 1000μg/kg in each year (lightly treated group) whereas 104 individuals received at least 1000μg/kg of blood factor for at least one year between 1982 and 1985 (heavily treated group). The individuals were assumed to be infected by the contaminated blood factor that they received during their treatment against hemophilia. Since the HIV infection status was determined by testing blood samples every 6-months, the HIV infection time is only known to have occurred between the times of the last negative and the first positive samples. Ninety-six individuals in the highly treated group, and 92 in the lightly treated group were infected with HIV during the study period. The primary aim was to measure the effect of levels of treatment on time to HIV seroconversion. The covariate of treatment is coded using a binary variable where x=1 if the subject is heavily treated and 0 otherwise. In the data set, time is measured in 6-months intervals where $L = 1$ denotes July 1,

1978. In this example, the subjects are not observed over time 18 (i.e. after 9 years). Hence we will describe the survival and hazard functions on [0,18]. We divide the support of infection time [0,18] into small bins of width 0.2, resulting in 90 small bins.



(a) Hazard Functions

(b) Survival Functions

Figure 7: Hemophiliacs data set: Estimated hazard and survival curves for the lightly and heavily treated groups with 90 % credible intervals (dashed and solid shaded, respectively) without proportionality assumption

Figure 6 displays the estimated hazard and survival functions for individuals in heavily and lightly treated groups under PH model, with highly treated group as the baseline. The log hazard ratio is calculated to be 0.90 with corresponding 90% credible interval (0.65,1.15) suggesting that the risk for HIV-seroconversion was larger in the group that received at least 1000μg/kg of blood factor. However, one should be careful as one might argue about the proportionality (hazards) assumption, see the Kaplan-Meier curves in Figure 6b. Therefore, the survival and hazard curves were estimated separately for each treatment group (without proportionality assumption): these are presented in Figure 7, the credible regions for the survival functions overlap until around time 8. Further, log hazard ratio was plotted in Figure 8: it decreases up to time 8 where 90% credible region includes 0 and after that time point it increases where the 90% credible region does not include 0 anymore. Hence, after around time 8 individuals in the heavily treated group have greater risk than individuals in the lightly treated group.

6.3 AIDS Data Set: ACTG019

Another data set for interval-censored data comes from an AIDS clinical trial, ACTG019 [13]. The clinical trial was designed to investigate the effect of zidovudine therapy on patients with an early stage HIV infection [37]. For this reason, 1650 patients were randomly assigned to three different groups: two different dosages of zidovudine and a deferred therapy group. The deferred

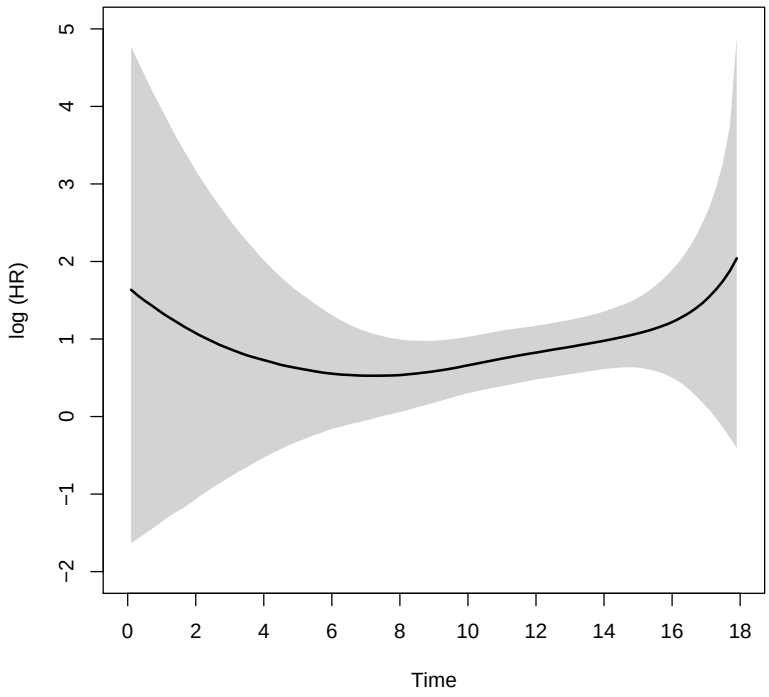


Figure 8: Hemophiliacs data set: Estimated log hazard ratio (heavily treated vs. lightly treated) with 90 % credible intervals without proportionality assumption

group corresponds to patients who started (500-mg) zidovudine therapy after their CD4 cell count decreased below 500 per cubic millimeter. In the other two groups the patients started to take one of the two dosages of zidovudine immediately after the randomization. After exclusion of some of the patients, there remained 541 subjects in the deferred therapy group, 538 in the 500-mg zidovudine group and 528 in the 1500-mg zidovudine group. The patients were followed until the development of AIDS or death. CD4 cell counts were observed periodically (every 2-4 weeks) and the times at which the CD4 cell counts decrease below 500, 400 and 300 per cubic millimeter were reported [37]. Here, we focus on the time, measured in months from randomization, until the CD4 cell counts decrease below 400 cells per cubic millimeter. Here, precise times are unknown but the time of the first visit when CD4 cell count was below 400 and the time of the preceding visit are known. Thus the time until CD4 cell count falls below 400 is interval-censored. The CD4 cell counts of 289, 267 and 230 patients in the deferred, 500-mg zidovudine and 1500-mg zidovudine therapy groups respectively, decreased below 400 during the trial.

The treatments were coded using two dummy variables (Z_1=0 and Z_2=0 for deferred therapy group, Z_1=1 and Z_2=0 for 500-mg zidovudine group, and Z_1=0 and Z_2=1 for 1500-mg zidovudine group).

The estimated hazard and survival functions for deferred therapy and two different levels of zidovudine therapy are also presented in Figure 9. The regression coefficients under Cox

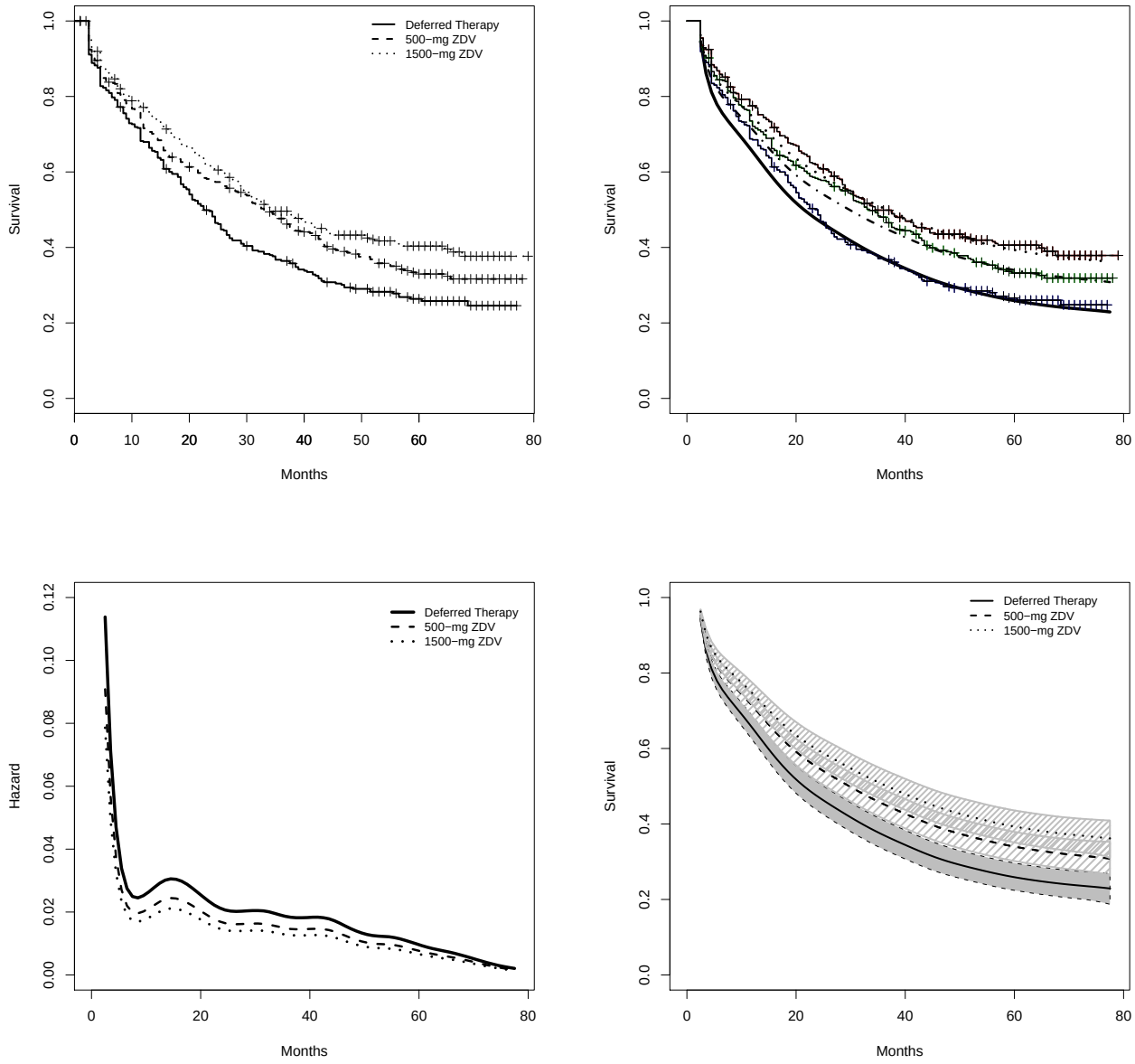
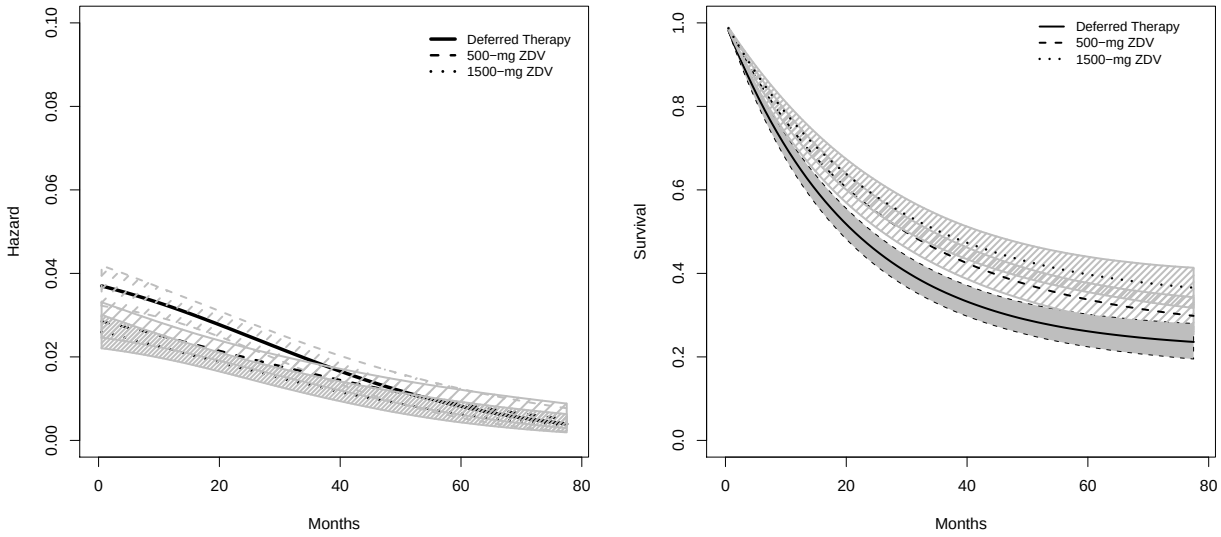


Figure 9: AIDS data set: Kaplan-Meier estimates and estimated smooth survival curves (above), estimated smooth hazard and survival curves under Cox PH model (below)

PH model were calculated as β_{500} = -0.22 with 90% credible interval (-0.37, -0.08) and β_{1500} = -0.37 with 90% credible interval (-0.52, -0.22). The Kaplan-Meier curves of the immediate treatment groups are crossing around month 30, but not with the Kaplan-Meier curve of the deferred therapy group. Again, this suggests that the proportional hazards hypothesis might not hold. Therefore, the hazard and the survival functions were also estimated in the three groups separately, see Figure 10. The survival curve estimates do not change markedly compared to the results under the PH hypothesis. However, now Figure 10a suggests that the patients under deferred therapy are significantly more at risk till about month 40. This approach is more insightful than the PH analysis that comes out with an averaged log hazards ratio to contrast treatments.



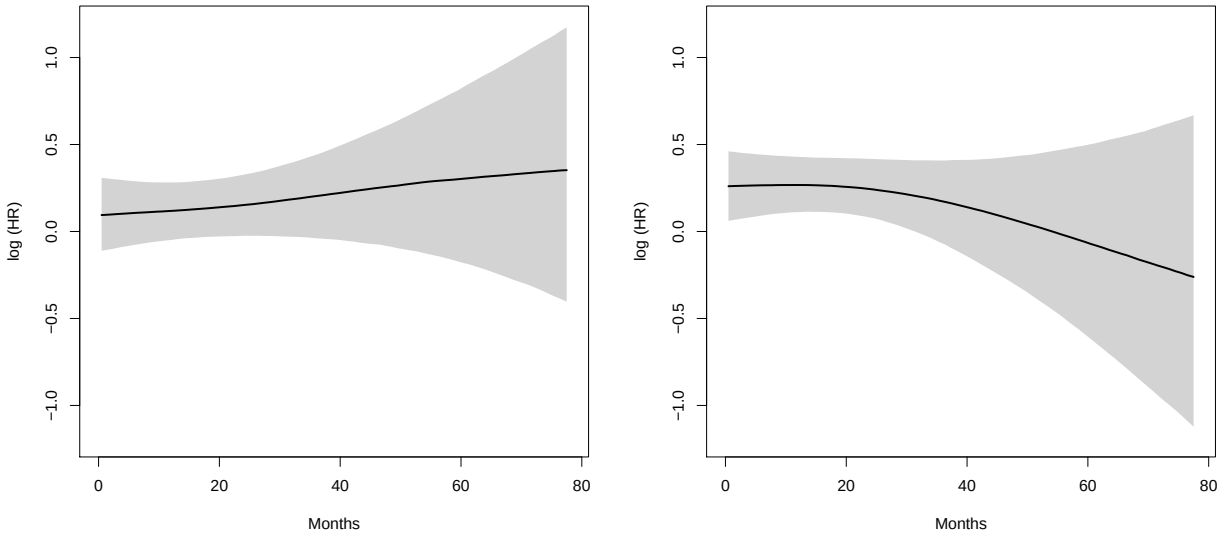
(a) Hazard Functions

(b) Survival Functions

Figure 10: AIDS data set: Estimated smooth hazard and survival curves without proportionality assumption

In Figure 9, the CD4 cell counts in the deferred therapy declined more quickly than those of the other two groups. Furthermore, the credible intervals for the 500-mg and 1500-mg ZDV therapy groups overlap, whereas the corresponding credible interval for the deferred-therapy group always lies below the other two groups.

The mean of the log hazard ratios with 90% credible regions are plotted for treatments pairs, 500-mg versus 1500-mg and deferred therapy versus 500-mg in Figure 11. The 90% credible region of the log hazard ratio does not include 0 up to around month 40 for the comparison deferred therapy versus 500-mg, whereas it always includes 0 for 500-mg versus 1500-mg therapy comparison. Additionally, none of the log hazard ratios functions are constant over time. As previously mentioned, these findings also support that a more insightful approach than the PH analysis may be more appropriate.



(a) 500-mg ZDV vs. 1500-mg ZDV

(b) Deferred therapy vs. 500-mg ZDV

Figure 11: AIDS data set: Estimated log hazard ratio with 90 % credible intervals without proportionality assumption

7 Discussion

Recently, much emphasis has been placed on non- or semi-parametric analysis of survival data. In clinical trials and longitudinal studies, interval-censored data are frequently obtained. In this research, we have extended a Bayesian density estimation procedure for grouped data to estimate the log-hazard ratios and the survival functions from interval-censored data. Our method produces estimates of log hazard ratios as well as smooth estimates of baseline survival and hazard functions. The performance of the proposed methodology was assessed under the proportional hazards hypothesis by means of an extensive simulation study combining different values of the interval widths and of the amount of right censoring. These two aspects were shown to play a very important role in the accuracy and the precision of the obtained estimates. Clearly, the proposed method provides very good estimates for the regression coefficients and successfully approximates the baseline survival function when the mean interval width is less than $\approx 1.3\sigma$.

The proposed methodology can be extended in several directions. A possible extension is the case where the observations belong to some clusters which necessitates to include a term accounting for the dependence within clusters, basically a shared frailty model for interval-censored data. Another interesting extension of the model for interval-censored data is the inclusion of time-varying coefficients.

Several applications were also presented. Despite the loss of information inherent to interval censoring, it was shown that one can detect situations where the hypothesis of hazards proportionality is arguable. Then, separate estimations of the survival and hazard functions are a workable alternative.

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Table 1: The point estimate with corresponding 90% Credible interval (CI), estimated coverage of 90% credible interval (EC90), estimated coverage of 80% credible interval (EC80), relative bias (Rbias in %), empirical standard error (ESE), root mean squared error (RMSE) for β_1 and β_2 under different amounts of right-censoring varying between 10% and 50% and different amounts of mean interval width varying between 6 (0.4σ) and 23 (1.6σ) for a sample of size n=300 in S=500 replications

		β_1=1.5							β_2=2.0						
r.cens.	width	Mean	90% CI	Rbias(%)	EC90	EC80	ESE	RMSE	Mean	90% CI	Rbias(%)	EC90	EC80	ESE	RMSE
10%	0.4σ	1.52	1.25 - 1.80	1.3	91	84	0.165	0.166	2.01	1.72 - 2.31	0.7	92	85	0.178	0.178
	0.7σ	1.51	1.24 - 1.81	0.9	89	80	0.183	0.188	2.01	1.68 - 2.34	0.4	89	80	0.189	0.194
	1.0σ	1.53	1.23 - 1.82	2.2	91	78	0.180	0.182	2.03	1.72 - 2.38	1.4	89	81	0.196	0.198
	1.3σ	1.50	1.17 - 1.82	0.2	89	77	0.199	0.200	2.02	1.70 - 2.38	0.8	90	80	0.212	0.213
	1.6σ	1.47	1.13 - 1.85	-1.9	87	75	0.216	0.218	1.96	1.55 - 2.36	-1.9	86	75	0.241	0.243
20%	0.4σ	1.55	1.28 - 1.88	3.3	89	80	0.180	0.188	2.04	1.76 - 2.37	1.8	91	82	0.184	0.190
	0.7σ	1.52	1.23 - 1.86	1.6	89	77	0.186	0.190	2.02	1.74 - 2.36	1.1	91	81	0.192	0.198
	1.0σ	1.54	1.24 - 1.85	1.7	88	77	0.197	0.201	2.02	1.70 - 2.38	1.2	90	80	0.204	0.205
	1.3σ	1.52	1.19 - 1.85	-1.0	89	79	0.199	0.199	1.99	1.64 - 2.34	-0.6	87	75	0.226	0.226
	1.6σ	1.48	1.17 - 1.84	-0.9	85	75	0.201	0.201	1.94	1.59 - 2.35	-2.8	86	75	0.228	0.235
35%	0.4σ	1.51	1.26 - 1.83	1.6	90	79	0.177	0.180	2.00	1.69 - 2.31	-0.1	91	80	0.189	0.190
	0.7σ	1.50	1.19 - 1.81	0.1	88	78	0.198	0.198	1.99	1.64 - 2.37	-0.5	86	75	0.200	0.200
	1.0σ	1.53	1.22 - 1.85	1.9	91	78	0.192	0.197	2.02	1.72 - 2.38	0.9	90	82	0.213	0.214
	1.3σ	1.48	1.15 - 1.95	1.6	88	77	0.215	0.216	1.95	1.61 - 2.35	-2.5	87	75	0.233	0.238
	1.6σ	1.45	1.12 - 1.78	0.4	86	75	0.246	0.248	1.96	1.57 - 2.40	-2.1	86	76	0.236	0.240
50%	0.4σ	1.54	1.21 - 1.88	2.8	89	80	0.208	0.212	2.05	1.68 - 2.40	2.3	90	80	0.206	0.214
	0.7σ	1.49	1.25 - 1.96	-0.7	88	77	0.217	0.232	1.98	1.74 - 2.41	-1.0	92	80	0.212	0.224
	1.0σ	1.58	1.23 - 1.95	4.2	88	78	0.222	0.236	2.06	1.70 - 2.48	2.8	87	78	0.219	0.227
	1.3σ	1.45	1.12 - 1.78	-3.5	91	81	0.206	0.213	1.89	1.53 - 2.23	-4.5	86	77	0.216	0.233
	1.6σ	1.53	1.16 - 1.95	1.9	90	80	0.254	0.255	1.99	1.61 - 2.41	-0.5	92	81	0.249	0.249

Table 2: The point estimate with corresponding 90% Credible interval (CI), estimated coverage of 90% credible interval (EC90), estimated coverage of 80% credible interval (EC80), relative bias (Rbias in %), empirical standard error (ESE), root mean squared error (RMSE) for estimated β_1 and β_2 under Cox PH model for different amounts of right-censoring varying between 10% and 50% and different amounts of mean interval width varying between 6 (0.4σ) and 23 (1.6σ) for a sample of size n=600 in S=500 replications

		β_1							β_2						
r.cens.	width	Mean	90% CI	Rbias (%)	EC90	EC80	ESE	RMSE	Mean	90% CI	Rbias (%)	EC90	EC80	ESE	RMSE
	0.4σ	1.50	1.29 - 1.70	0.2	90	79	0.125	0.125	2.02	1.81 - 2.25	1.0	90	79	0.134	0.135
	0.7σ	1.50	1.29 - 1.71	0.1	90	82	0.121	0.121	2.00	1.79 - 2.22	0.1	91	82	0.133	0.133
10%	1.0σ	1.49	1.30 - 1.70	-0.4	92	82	0.125	0.125	2.00	1.80 - 2.22	0.1	93	84	0.134	0.134
	1.3σ	1.47	1.23 - 1.70	-1.8	87	79	0.140	0.145	1.98	1.71 - 2.26	-1.6	87	77	0.157	0.160
	1.6σ	1.42	1.16 - 1.67	-3.4	87	78	0.150	0.169	1.94	1.69 - 2.20	-4.1	86	77	0.158	0.158
	0.4σ	1.51	1.31 - 1.71	0.6	90	82	0.121	0.121	2.01	1.82 - 2.23	0.4	92	83	0.130	0.130
	0.7σ	1.51	1.30 - 1.73	0.4	90	82	0.125	0.125	2.00	1.77 - 2.23	0.1	89	79	0.140	0.140
20%	1.0σ	1.49	1.28 - 1.73	-0.7	87	78	0.138	0.139	1.99	1.76 - 2.24	-0.6	89	82	0.140	0.141
	1.3σ	1.49	1.25 - 1.70	-3.2	87	75	0.139	0.147	1.97	1.70 - 2.20	-1.3	87	78	0.150	0.162
	1.6σ	1.45	1.22 - 1.68	-3.7	87	77	0.137	0.153	1.93	1.65 - 2.23	-3.2	86	75	0.152	0.172
	0.4σ	1.52	1.33 - 1.72	1.6	92	81	0.124	0.126	2.01	1.79 - 2.24	0.7	90	81	0.133	0.133
	0.7σ	1.51	1.30 - 1.74	0.9	89	79	0.130	0.130	2.02	1.79 - 2.25	0.8	89	78	0.143	0.144
35%	1.0σ	1.50	1.26 - 1.75	0.1	87	80	0.142	0.139	1.99	1.76 - 2.23	-0.7	90	82	0.148	0.149
	1.3σ	1.47	1.25 - 1.68	-2.4	89	78	0.138	0.143	1.95	1.72 - 2.20	-2.8	88	75	0.145	0.156
	1.6σ	1.46	1.23 - 1.70	-2.7	90	79	0.141	0.147	1.96	1.71 - 2.25	-1.7	86	75	0.166	0.175
	0.4σ	1.53	1.30 - 1.78	2.2	88	78	0.138	0.142	2.03	1.80 - 2.27	1.4	89	79	0.140	0.143
	0.7σ	1.53	1.31 - 1.76	2.0	92	81	0.140	0.143	2.01	1.80 - 2.23	0.5	93	84	0.144	0.144
50%	1.0σ	1.52	1.27 - 1.77	1.1	90	80	0.153	0.154	2.01	1.77 - 2.27	0.4	90	79	0.157	0.157
	1.3σ	1.53	1.27 - 1.78	2.0	89	81	0.161	0.164	2.00	1.73 - 2.27	-0.1	90	79	0.169	0.169
	1.6σ	1.52	1.25 - 1.82	1.6	88	77	0.181	0.182	1.98	1.70 - 2.26	-1.1	89	79	0.175	0.177

Table 3: The point estimate with corresponding 90% Credible interval (CI), estimated coverage of 90% credible interval (EC90), estimated coverage of 80% credible interval (EC80), relative bias (Rbias in %), empirical standard error (ESE), root mean squared error (RMSE) for estimated β_1 and β_2 under Cox PH model for 0% right-censoring and different amounts of mean interval width varying between 6 (0.4σ) and 23 (1.6σ) for a sample of size n=300 and n=600 in S=500 replications

		β_1							β_2						
n	width	Mean	90% CI	Rbias (%)	EC90	EC80	ESE	RMSE	Mean	90% CI	Rbias (%)	EC90	EC80	ESE	RMSE
	0.4σ	1.49	1.23 - 1.77	-0.3	90	80	0.168	0.167	2.00	1.73 - 2.30	0.1	90	80	0.179	0.179
	0.7σ	1.51	1.24 - 1.79	0.6	90	80	0.176	0.176	2.01	1.70 - 2.29	0.7	90	80	0.185	0.185
300	1.0σ	1.48	1.22 - 1.79	-1.6	90	80	0.175	0.177	1.98	1.69 - 2.30	-0.9	91	83	0.192	0.193
	1.3σ	1.48	1.20 - 1.79	-1.4	89	81	0.187	0.188	1.98	1.67 - 2.31	-0.8	91	81	0.201	0.201
	1.6σ	1.47	1.21 - 1.78	-1.7	93	81	0.186	0.188	1.96	1.65 - 2.30	-1.8	91	80	0.200	0.204
	0.4σ	1.49	1.30 - 1.67	-0.9	92	79	0.115	0.129	1.99	1.77 - 2.20	-0.4	89	79	0.129	0.129
	0.7σ	1.49	1.29 - 1.69	-0.7	90	80	0.121	0.121	1.99	1.78 - 2.22	-0.3	90	80	0.136	0.136
600	1.0σ	1.49	1.31 - 1.67	-1.0	93	84	0.118	0.119	1.99	1.76 - 2.20	-0.7	91	82	0.130	0.131
	1.3σ	1.48	1.28 - 1.70	-1.5	90	79	0.129	0.130	1.97	1.74 - 2.20	-1.6	90	79	0.138	0.142
	1.6σ	1.47	1.26 - 1.67	-1.9	91	83	0.129	0.132	1.95	1.72 - 2.18	-2.4	91	81	0.136	0.144

Table 4: Target, mean estimated values, 90% credible interval, relative bias, 90% and 80% coverages, empirical standard error and root mean squared error for ζ for n=300

t_{cens}	Target	int.width	Mean	90% CI	Rbias	EC90	EC80	ESE	RMSE
		0.4σ	0.87	0.81 - 0.93	-3.6	78	67	0.036	0.049
		0.7σ	0.86	0.78 - 0.92	-4.8	65	48	0.039	0.068
83	0.90	1.0σ	0.84	0.77 - 0.91	-6.9	54	42	0.041	0.075
		1.3σ	0.83	0.76 - 0.90	-8.6	46	36	0.047	0.091
		1.6σ	0.80	0.72 -0.88	-11.0	31	21	0.050	0.111
		0.4σ	0.75	0.68 - 0.82	-6.0	71	58	0.044	0.065
		0.7σ	0.72	0.65 - 0.81	-8.2	55	41	0.048	0.072
77	0.80	1.0σ	0.71	0.62 - 0.79	-11.9	40	27	0.052	0.094
		1.3σ	0.68	0.59 - 0.76	-15.3	27	15	0.053	0.133
		1.6σ	0.64	0.54 - 0.75	-19.8	14	10	0.062	0.170
		0.4σ	0.60	0.53 - 0.69	-8.6	68	55	0.048	0.074
		0.7σ	0.57	0.48 - 0.66	-13.4	47	32	0.056	0.104
71	0.65	1.0σ	0.53	0.45 - 0.62	-18.8	24	14	0.057	0.118
		1.3σ	0.51	0.41 - 0.60	-23.1	13	7	0.056	0.148
		1.6σ	0.46	0.38 - 0.56	-29.8	9	5	0.055	0.204
		0.4σ	0.45	0.36 - 0.54	-10.6	64	48	0.059	0.079
		0.7σ	0.41	0.33 - 0.51	-17.0	40	29	0.056	0.102
63	0.50	1.0σ	0.37	0.29 - 0.46	-25.6	20	12	0.051	0.137
		1.3σ	0.35	0.26 - 0.43	-30.5	12	6	0.051	0.161
		1.6σ	0.31	0.23 - 0.40	-36.9	9	4	0.051	0.191

Table 5: Target, mean estimated values, 90% credible interval, relative bias, 90% and 80% coverages, empirical standard error and root mean squared error for ζ for n=600

t_{cens}	Target	int.width	Mean	90% CI	Rbias	EC90	EC80	ESE	RMSE
		0.4σ	0.87	0.83 - 0.91	-3.5	63	51	0.024	0.036
		0.7σ	0.85	0.80 - 0.89	-6.1	31	21	0.029	0.063
83	0.90	1.0σ	0.83	0.78 - 0.88	-8.4	20	10	0.031	0.082
		1.3σ	0.82	0.76 - 0.88	-9.4	17	10	0.034	0.092
		1.6σ	0.79	0.72 -0.86	-10.9	9	4	0.040	0.106
		0.4σ	0.75	0.70 - 0.80	-6.1	54	37	0.031	0.058
		0.7σ	0.72	0.66 - 0.77	-10.2	20	11	0.035	0.089
77	0.80	1.0σ	0.70	0.64 - 0.75	-13.0	7	3	0.034	0.109
		1.3σ	0.66	0.60 - 0.73	-16.2	4	2	0.043	0.142
		1.6σ	0.63	0.56 - 0.70	-20.5	0	0	0.042	0.170
		0.4σ	0.60	0.55 - 0.66	-8.2	53	36	0.035	0.064
		0.7σ	0.56	0.50 - 0.63	-14.4	14	8	0.039	0.102
71	0.65	1.0σ	0.53	0.46 - 0.59	-20.2	1	1	0.037	0.138
		1.3σ	0.50	0.43 - 0.56	-24.2	1	0	0.042	0.166
		1.6σ	0.47	0.40 - 0.54	-28.5	1	0	0.042	0.192
		0.4σ	0.44	0.38 - 0.50	-11.9	49	37	0.034	0.068
		0.7σ	0.41	0.35 - 0.48	-20.4	10	6	0.034	0.107
63	0.50	1.0σ	0.37	0.30 - 0.43	-26.7	3	1	0.038	0.138
		1.3σ	0.34	0.28 - 0.41	-31.2	1	0	0.038	0.160
		1.6σ	0.32	0.26 - 0.39	-36.3	0	0	0.036	0.185

Table 6: The relative bias (Rbias in %), empirical standard errors (ESE) and root mean squared error (RMSE) for baseline survival at selected quantiles (5%, 15%, 25%, 35%, 50%, 60%, 75%, 85% and 88%) of T under Cox PH model for different right-censoring amounts between 10% and 50% and different mean interval width (varying between 0.4σ and 1.6σ) for a sample of size n=300 in S=500 replications

		interval width														
		$0.4\sigma \cong 6$			$0.7\sigma \cong 10$			$1.0\sigma \cong 15$			$1.3\sigma \cong 19$			$1.6\sigma \cong 23$		
t_{cens}		Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE
83	S(39)	-0.3	0.010	0.519	-0.1	0.010	0.520	-0.3	0.011	0.519	-0.3	0.012	0.519	-0.4	0.013	0.518
	S(49)	-1.0	0.023	0.436	-0.4	0.024	0.441	-0.8	0.024	0.439	-1.1	0.027	0.438	-1.8	0.030	0.431
	S(55)	-1.6	0.033	0.363	-0.8	0.034	0.367	-1.3	0.034	0.364	-2.2	0.037	0.360	-3.5	0.038	0.345
	S(59)	-2.0	0.038	0.317	-1.1	0.039	0.320	-1.4	0.040	0.317	-3.0	0.043	0.313	-4.4	0.049	0.309
	S(65)	-1.5	0.042	0.291	-0.9	0.045	0.296	0.6	0.044	0.295	-2.5	0.048	0.294	-3.0	0.053	0.296
	S(69)	0.3	0.041	0.315	0.8	0.044	0.309	4.8	0.043	0.305	1.4	0.048	0.309	2.7	0.050	0.310
	S(75)	7.7	0.038	0.379	10.7	0.040	0.379	19.3	0.040	0.367	19.3	0.044	0.363	26.3	0.048	0.356
	S(80)	19.9	0.035	0.447	31.1	0.037	0.435	43.6	0.039	0.422	55.6	0.046	0.411	73.1	0.054	0.396
	S(81)	22.8	0.035	0.457	37.1	0.037	0.445	50.2	0.040	0.433	66.8	0.047	0.418	87.8	0.056	0.399
77	S(39)	-0.1	0.010	0.520	-0.1	0.010	0.521	-0.2	0.011	0.520	-0.4	0.012	0.518	-0.6	0.012	0.517
	S(49)	-0.3	0.024	0.442	-0.5	0.025	0.439	-0.8	0.027	0.440	-1.8	0.029	0.431	-2.6	0.031	0.427
	S(55)	-0.4	0.034	0.366	-0.9	0.036	0.367	-1.2	0.039	0.364	-3.2	0.042	0.358	-4.4	0.044	0.351
	S(59)	-0.2	0.039	0.324	-1.0	0.043	0.320	-0.8	0.044	0.324	-3.4	0.050	0.315	-4.3	0.051	0.315
	S(65)	1.6	0.044	0.293	0.9	0.048	0.294	3.4	0.047	0.291	1.5	0.053	0.295	2.5	0.053	0.296
	S(69)	5.2	0.044	0.305	5.9	0.047	0.306	10.8	0.046	0.299	12.1	0.052	0.298	15.4	0.053	0.299
	S(75)	16.8	0.042	0.368	24.8	0.045	0.359	34.7	0.047	0.342	49.3	0.054	0.330	58.9	0.059	0.319
71	S(39)	-0.1	0.010	0.521	-0.04	0.011	0.521	-0.2	0.011	0.519	-0.3	0.013	0.518	-0.6	0.013	0.516
	S(49)	-0.4	0.024	0.441	-0.1	0.028	0.444	-1.2	0.026	0.436	-1.8	0.033	0.433	-2.8	0.039	0.426
	S(55)	-0.7	0.034	0.368	0.04	0.043	0.369	-1.1	0.036	0.364	-2.1	0.048	0.364	-2.6	0.054	0.359
	S(59)	-0.2	0.040	0.323	1.1	0.050	0.327	0.7	0.042	0.325	0.5	0.054	0.326	1.0	0.057	0.329
	S(65)	3.9	0.046	0.293	7.8	0.051	0.296	10.4	0.047	0.299	14.0	0.053	0.299	17.0	0.054	0.300
	S(69)	11.1	0.048	0.299	18.7	0.047	0.294	24.9	0.050	0.287	33.4	0.053	0.292	38.8	0.055	0.302
65	S(39)	-0.1	0.011	0.521	0.1	0.011	0.521	-0.2	0.012	0.519	-0.1	0.015	0.520	-0.3	0.016	0.519
	S(49)	-0.5	0.027	0.440	-0.4	0.027	0.441	-0.5	0.029	0.441	-0.7	0.043	0.441	-0.5	0.045	0.442
	S(55)	-0.4	0.039	0.369	0.6	0.039	0.374	2.1	0.039	0.378	2.8	0.055	0.384	4.2	0.055	0.394
	S(59)	1.6	0.044	0.331	4.4	0.045	0.338	7.6	0.043	0.348	9.3	0.055	0.360	12.3	0.054	0.370

Table 7: The relative bias (Rbias in %), empirical standard errors (ESE) and root mean squared error (RMSE) for baseline survival at selected quantiles (5%, 15%, 25%, 35%, 50%, 60%, 75%, 85% and 88%) of T under Cox PH model for different right-censoring amounts between 10% and 50% and different mean interval widths (varying between 0.4σ and 1.6σ) for a sample of size n=600 in S=500 replications

		interval width														
		$0.4\sigma \cong 6$			$0.7\sigma \cong 10$			$1.0\sigma \cong 15$			$1.3\sigma \cong 19$			$1.6\sigma \cong 23$		
t_{cens}		Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE	Rbias (%)	ESE	RMSE
83	S(39)	-0.3	0.007	0.519	-0.4	0.007	0.518	-0.3	0.008	0.518	-0.3	0.009	0.518	-0.7	0.009	0.516
	S(49)	-0.8	0.017	0.438	-1.0	0.017	0.437	-1.0	0.018	0.437	-1.3	0.021	0.434	-2.4	0.021	0.429
	S(55)	-1.4	0.025	0.364	-1.7	0.024	0.359	-1.7	0.25	0.362	-2.6	0.029	0.357	-4.7	0.030	0.348
	S(59)	-2.0	0.030	0.315	-2.4	0.028	0.316	-2.6	0.028	0.317	-4.0	0.033	0.313	-6.7	0.035	0.308
	S(65)	-3.1	0.033	0.294	-3.8	0.031	0.290	-3.9	0.030	0.292	-5.5	0.035	0.291	-7.6	0.038	0.292
	S(69)	-3.2	0.032	0.314	-3.6	0.030	0.319	-2.7	0.030	0.315	-3.4	0.034	0.319	-3.3	0.036	0.320
	S(75)	1.1	0.027	0.392	3.7	0.026	0.386	9.8	0.028	0.377	14.1	0.031	0.371	20.8	0.035	0.362
	S(80)	15.1	0.023	0.451	25.8	0.025	0.440	43.2	0.028	0.422	56.6	0.032	0.411	74.7	0.039	0.389
	S(81)	19.9	0.023	0.460	33.3	0.026	0.446	54.4	0.029	0.427	70.7	0.033	0.412	92.3	0.040	0.397
77	S(39)	-0.3	0.007	0.519	-0.3	0.007	0.518	-0.4	0.008	0.518	-0.5	0.008	0.399	-0.9	0.009	0.396
	S(49)	-0.8	0.017	0.438	-0.8	0.018	0.438	-1.2	0.018	0.435	-2.0	0.020	0.313	-3.0	0.022	0.307
	S(55)	-1.5	0.024	0.362	-1.5	0.025	0.363	-2.5	0.025	0.359	-3.0	0.028	0.254	-3.9	0.031	0.247
	S(59)	-2.1	0.028	0.318	-2.3	0.029	0.317	-3.8	0.030	0.312	-3.8	0.033	0.236	-4.1	0.036	0.301
	S(65)	-2.4	0.030	0.290	-2.3	0.032	0.290	-2.8	0.034	0.292	1.0	0.036	0.268	-0.6	0.035	0.267
	S(69)	-0.1	0.029	0.312	1.9	0.032	0.309	4.9	0.034	0.305	8.0	0.035	0.296	11.4	0.034	0.294
	S(75)	14.4	0.028	0.371	25.3	0.032	0.355	39.6	0.034	0.337	50.1	0.038	0.328	60.8	0.037	0.312
71	S(39)	-0.3	0.007	0.519	-0.3	0.007	0.519	-0.3	0.008	0.519	-0.4	0.013	0.518	-0.6	0.009	0.322
	S(49)	-0.8	0.017	0.439	-0.8	0.017	0.437	-1.2	0.019	0.434	-1.8	0.033	0.433	-3.6	0.022	0.231
	S(55)	-1.5	0.025	0.360	-1.7	0.025	0.362	-3.0	0.028	0.355	-2.1	0.048	0.364	-5.0	0.031	0.196
	S(59)	-1.7	0.030	0.320	-2.1	0.030	0.316	-2.9	0.034	0.316	0.5	0.054	0.326	-1.9	0.033	0.196
	S(65)	1.6	0.034	0.291	3.7	0.034	0.292	7.9	0.035	0.292	14.0	0.053	0.299	16.0	0.036	0.214
	S(69)	10.2	0.034	0.301	17.5	0.034	0.291	27.8	0.035	0.290	33.4	0.053	0.292	41.9	0.038	0.234
65	S(39)	-0.2	0.008	0.519	-0.2	0.007	0.520	-0.2	0.008	0.519	-0.3	0.009	0.185	-0.6	0.010	0.182
	S(49)	-0.8	0.020	0.438	-1.1	0.019	0.436	-1.9	0.022	0.432	-2.4	0.024	0.117	-2.8	0.026	0.113
	S(55)	-1.2	0.029	0.364	-1.7	0.028	0.361	-1.7	0.032	0.360	-0.1	0.032	0.129	1.1	0.032	0.121
	S(59)	0.3	0.034	0.321	1.6	0.032	0.328	4.3	0.034	0.336	7.7	0.034	0.149	10.0	0.033	0.136

Table 8: The coverage estimates of 90% credible intervals for baseline survival function at selected quantiles (5%, 15%, 25%, 35%, 50%, 60%, 75%, 85% and 88%) of T under Cox PH model for different right-censoring amounts between 10% and 50% and different mean interval widths between $6(0.4\sigma)$ and $23(1.6\sigma)$ for sample sizes of n=300 and 600 in S=500 replications

			n=300					n=600				
			int. width					int. width				
r.cens.	t_{cens}		$0.4\sigma \cong 6$	$0.7\sigma \cong 10$	$1.0\sigma \cong 15$	$1.3\sigma \cong 19$	$1.6\sigma \cong 23$	$0.4\sigma \cong 6$	$0.7\sigma \cong 10$	$1.0\sigma \cong 15$	$1.3\sigma \cong 19$	$1.6\sigma \cong 23$
10%	83	S(39)	90	90	92	90	88	90	87	87	85	85
		S(49)	90	91	90	89	83	88	89	89	80	86
		S(55)	90	91	90	87	80	87	88	90	75	87
		S(59)	90	90	90	87	80	84	88	88	76	88
		S(65)	93	93	92	89	88	85	87	89	86	82
		S(69)	94	94	88	90	89	87	89	93	92	88
		S(75)	85	89	68	72	58	91	91	82	65	64
		S(80)	76	72	51	40	28	76	74	66	62	46
		S(81)	76	67	50	36	26	71	69	60	56	35
20%	77	S(39)	89	91	89	88	84	90	89	88	92	93
		S(49)	91	90	91	83	78	89	89	89	88	88
		S(55)	92	90	90	82	77	88	89	86	89	92
		S(59)	92	90	92	84	82	88	87	82	92	87
		S(65)	92	90	89	89	89	91	90	90	93	92
		S(69)	87	87	77	76	70	93	90	88	81	75
		S(75)	74	61	47	25	16	70	35	11	30	31
35%	71	S(39)	89	89	91	87	84	89	89	87	89	87
		S(49)	91	87	89	80	73	88	89	86	87	86
		S(55)	91	88	92	83	80	87	90	91	88	86
		S(59)	91	88	90	88	87	87	90	86	93	90
		S(65)	88	82	70	61	52	88	87	70	65	53
		S(69)	76	55	40	21	14	70	59	52	25	23
50%	65	S(39)	88	89	90	84	81	87	91	91	90	86
		S(49)	88	90	90	76	76	87	88	86	79	82
		S(55)	89	88	90	79	77	88	87	87	90	90
		S(59)	88	83	69	62	49	89	91	79	66	51

Table 9: The relative bias (Rbias in %), empirical standard errors(ESE) and root mean squared error (RMSE) for baseline survival at selected quantiles (5%, 15%, 25%, 35%, 50%, 60%, 75%, 85% and 88%) of T under Cox PH model for 0% right-censoring and different amounts of mean interval width (varying between 0.4σ and 1.6σ) for a sample of size n=300 and 600 in S=500 replications

		interval width																			
		$0.4\sigma \cong 6$				$0.7\sigma \cong 10$				$1.0\sigma \cong 15$				$1.3\sigma \cong 19$				$1.6\sigma \cong 23$			
n		Rbias (%)	ESE	RMSE	EC90	Rbias (%)	ESE	RMSE	EC90	Rbias (%)	ESE	RMSE	EC90	Rbias (%)	ESE	RMSE	EC90	Rbias (%)	ESE	RMSE	EC90
	S(39)	-0.4	0.007	0.631	89	-0.3	0.007	0.632	89	-0.3	0.007	0.632	87	-0.5	0.008	0.630	87	-0.6	0.008	0.629	87
	S(49)	-1.2	0.016	0.543	90	-1.1	0.018	0.544	89	-1.2	0.016	0.542	87	-1.5	0.018	0.541	87	-1.9	0.018	0.540	89
	S(55)	-2.0	0.023	0.462	89	-2.0	0.025	0.462	89	-2.2	0.23	0.461	85	-2.8	0.025	0.458	87	-3.0	0.024	0.457	89
	S(59)	-2.7	0.027	0.398	90	-2.9	0.028	0.399	88	-3.1	0.027	0.397	85	-3.9	0.028	0.392	87	-4.1	0.027	0.392	89
	S(65)	-4.0	0.031	0.330	90	-4.4	0.023	0.331	87	-4.5	0.029	0.329	87	-5.4	0.029	0.328	87	-5.3	0.028	0.330	92
300	S(69)	-4.7	0.030	0.321	89	-5.2	0.018	0.320	88	-2.7	0.028	0.321	89	-5.6	0.028	0.320	91	-5.0	0.027	0.321	94
	S(75)	-5.0	0.025	0.361	92	-5.0	0.017	0.363	92	-3.4	0.024	0.377	94	-2.9	0.023	0.360	93	-0.4	0.023	0.357	93
	S(80)	-2.5	0.019	0.409	93	-1.1	0.015	0.408	92	2.8	0.019	0.422	93	5.5	0.018	0.402	87	10.9	0.018	0.398	85
	S(81)	-1.4	0.018	0.417	93	0.4	0.017	0.416	91	5.0	0.017	0.427	91	8.4	0.017	0.409	81	14.5	0.017	0.405	80
	S(83)	1.6	0.016	0.440	93	4.6	0.015	0.439	90	10.7	0.015	0.435	86	15.7	0.015	0.432	72	23.8	0.015	0.426	70
	S(87)	13.0	0.012	0.464	83	19.3	0.011	0.461	78	30.0	0.012	0.457	66	39.8	0.012	0.453	50	53.9	0.012	0.449	35
	S(39)	-0.3	0.010	0.632	87	-0.3	0.010	0.632	87	-0.5	0.011	0.630	89	-0.5	0.011	0.630	86	-0.8	0.011	0.628	85
	S(49)	-1.1	0.022	0.543	86	-0.9	0.024	0.545	87	-1.5	0.024	0.542	87	-1.4	0.025	0.541	84	-1.7	0.023	0.540	82
	S(55)	-1.9	0.031	0.462	85	-1.8	0.033	0.463	86	-2.7	0.032	0.459	86	-2.5	0.034	0.463	80	-2.9	0.031	0.457	79
	S(59)	-2.7	0.036	0.401	85	-2.5	0.038	0.401	86	-3.7	0.037	0.394	85	-3.4	0.038	0.396	79	-3.7	0.035	0.395	77
	S(65)	-3.9	0.040	0.329	83	-3.5	0.041	0.333	83	-4.9	0.039	0.331	84	-4.1	0.041	0.330	81	-4.1	0.037	0.331	81
600	S(69)	-4.3	0.039	0.320	82	-3.6	0.039	0.320	84	-4.8	0.038	0.322	84	-3.3	0.040	0.326	87	-2.9	0.036	0.319	88
	S(75)	-2.7	0.032	0.362	87	-1.1	0.033	0.358	90	-1.0	0.032	0.358	91	2.4	0.034	0.354	92	4.0	0.031	0.354	93
	S(80)	3.3	0.025	0.403	92	6.5	0.025	0.402	93	9.0	0.025	0.399	93	15.4	0.027	0.393	92	19.0	0.025	0.391	87
	S(81)	5.4	0.023	0.411	92	9.0	0.024	0.409	93	12.2	0.023	0.407	92	19.4	0.026	0.403	90	23.7	0.024	0.397	84
	S(83)	10.9	0.020	0.436	92	15.7	0.021	0.431	93	20.6	0.021	0.428	89	29.8	0.023	0.422	84	35.4	0.021	0.420	72
	S(87)	29.8	0.015	0.457	89	37.8	0.016	0.455	84	47.8	0.016	0.451	73	63.3	0.018	0.445	56	73.1	0.017	0.442	35

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