Semiparametric analysis of clustered interval-censored survival data
using Soft Bayesian Additive Regression Trees (SBART)

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ABSTRACT: Popular parametric and semiparametric hazards regression models for clustered survival data are inappropriate and inadequate when the unknown effects of different covariates and clustering are complex. This calls for a flexible modeling framework to yield efficient survival prediction. Moreover, for some survival studies involving time to occurrence of some asymptomatic events, survival times are typically interval censored between consecutive clinical inspections. In this article, we propose a robust semiparametric model for clustered interval-censored survival data under a paradigm of Bayesian ensemble learning, called Soft Bayesian Additive Regression Trees or SBART (Linero and Yang, 2018), which combines multiple sparse (soft) decision trees to attain excellent predictive accuracy. We develop a novel semiparametric hazards regression model by modeling the hazard function as a product of a parametric baseline hazard function and a nonparametric component that uses SBART to incorporate clustering, unknown functional forms of the main effects, and interaction effects of various covariates. In addition to being applicable for left-censored, right-censored, and interval-censored survival data, our methodology is implemented using a data augmentation scheme which allows for existing Bayesian backfitting algorithms to be used. We illustrate the practical implementation and advantages of our method via simulation studies and an analysis of a prostate cancer surgery study where dependence on the experience and skill level of the physicians leads to clustering of survival times. We conclude by discussing our method’s applicability in studies involving high dimensional data with complex underlying associations.

Key words: Bayesian Additive Regression Trees, Survival analysis, semiparametric, baseline hazard.
1 Introduction

Interval censored survival data arise frequently in asymptomatic diseases that have no immediate outward symptoms (Sun, 2006) and the event of interest, such as device failure or relapse of a disease after initial treatment, is known to occur only between two consecutive inspection times. For instance, recurrence of biomarkers are often detected either during scheduled clinic visits or via some invasive procedures/diagnostic tests causing the survival times to such events to be interval-censored within consecutive inspection times with opposite diagnosis/test results. Our motivation behind this article is a follow up study to compare two competing surgical techniques, Robotic versus non-robotic Radical Retropubic Prostatectomy (RRP), for prostate removal in terms of the patients’ time to recurrence (survival time of interest) of Prostate Specific Antigen (PSA) after the surgery. The PSA level in the blood after prostate removal surgery is 0.0 ng/ml, and a PSA recurrence is defined as the time after surgery at which the PSA level exceeds 0.2 ng/ml. Genitourinary surgeons and oncologists are particularly interested in whether a surgery using a robotic device improves the time to PSA recurrence compared to non-robotic surgery for removing the cancerous prostate. Because continuous monitoring of PSA is not feasible, the time to PSA recurrence for each patient is interval censored between consecutive blood tests. Further, any assumed parametric model for the regression effects of various baseline covariates on risk/hazard of time to PSA recurrence is restrictive and difficult to justify on subject-matter grounds. Hence, using a flexible modeling approach which accommodates possible non-linearity and multi-way interactions among the variables is prudent. Moreover, we expect these survival times to be clustered due to the possible presence of unobserved surgeon effects, such as the surgeon’s experience, skill, and access/familiarity with modern medical technology. Hence, we need to account for an appropriate within cluster association (in this case, due to surgeon effects) to obtain efficient and appropriate models for survival prediction.

Most semiparametric models for interval-censored survival data use either an Accelerated Failure Time (AFT) model (Hanson et. al, 2007) or a proportional hazards model (Sun, 2006; Ghosh and Sinha, 2001). However, accelerated failure time models do not account for error heteroscedasticity and, in practice, survival data can often violate the restrictive assumption of proportional hazards. In addition,
dependence on factors such as experience and skill level of physicians and clinics often lead to clustering of survival data due to random clinician/clinical site effects. Some examples of clustered interval-censored survival data include the National Aeronautics and Space Administration’s hypobaric decompression sickness study (HDSD) (Conkin et. al, 1992; Conkin and Powell, 2001) and the Lymphatic Filariasis study (Dryer G, Addiss D, 2006). However, failure to account for clustering effects may produce misleading results and, in particular, inaccurate estimation of the precision of the estimated parameters. Most methods for analyzing clustered survival data use frailty random effects (Oakes, 1982) to accommodate within-cluster association as well as between-cluster heterogeneity. Goethals et. al (2009) used a proportional hazards model with a Gamma frailty to analyze clustered interval-censored survival data.

However, main regression effects and effects of interaction among different covariates in survival data are often time-dependent and are potentially more complex than what can be envisioned by a prespecified parametric model of covariate effects on either the hazard, the median, or the mean. This calls for a flexible modeling framework for covariate effects. Some of the proposed approaches to accommodate such complex regression relationships include the boosting proportional hazards model of Li and Luan (2005), bagging (Hothorn et. al, 2004, 2006) and random survival forests (Ishwaran et. al, 2008). Using a Gaussian process to incorporate nonparametric covariate effects, Fernandez et. al (2016) presented a Bayesian semiparametric survival model centered on a parametric baseline hazard model in a fashion similar to ours.

Boosting is an example of ensemble learning, which combines multiple weak learners to attain both high stability and a flexible model. The Bayesian additive regression trees (BART) framework proposed by Chipman et. al (2010) is a Bayesian framework for tree-based ensemble models. BART is a computationally efficient and flexible technique, and can accommodate complex non-linear regression relationships. Since its introduction, the BART framework has been extended to account for many different types of model specifications, including semiparametric regression under heteroscedasticity (Pratola et. al, 2017), log-linear models (Murray, 2017), multivariate and multi-scale data (Linero et. al, 2020), causal inference (Hahn et. al, 2020), and varying coefficient models (Deshpande et. al, 2020). For systematic reviews of Bayesian tree-based methods and BART, see Linero (2017) and Hill et. al (2020). A recent surge of
interest in BART lies in its applications for analyzing survival data. By modeling nonparametric effects of covariates on the survival times through the tree ensembles, Bonato et. al (2011) employed BART for survival prediction in high dimensional genetic studies under three specific models - Weibull regression, proportional hazards regression, and Accelerated Failure Time models. Sparapani et. al (2016) addressed discrete-time survival data with the discrete-time hazard being modeled nonparametrically via BART. However, this approach is aimed essentially at discrete-time survival data and requires the specification of a finite number of possible failure times in order to be used for continuous survival data, and the computational cost increases rapidly for even a moderate increase in the number of possible failure times. Despite this stream of research, to the best of our knowledge, there are no applications of BART for analysis of interval censored survival data. Additionally, two potential shortcomings of the usual BART framework include the lack of smoothness of the estimated regression function and sensitivity to the curse of dimensionality (Linero, 2018). Linero and Yang (2018) recently addressed these drawbacks with an extension of BART called Soft BART (SBART), which provides a considerable improvement over BART by employing an ensemble of “soft” decision trees that can adapt to the unknown smoothness level of the true regression function, and can also remove irrelevant predictors.

In this paper, we present a flexible semiparametric model for interval-censored survival data using BART. Our approach models the hazard function of the survival times as a product of (a): a parametric baseline hazard which represents the “guess/center” of the actual hazard and (b): a nonparametric component modeled using SBART to account for the possible deviation from the guess/center model at (a) as well as complex time-dependent effects of covariates and cluster-specific random effects on hazard. We use a data augmentation scheme based on “thinning” a Poisson process (Adams et. al, 2009) to construct an efficient Markov chain Monte Carlo algorithm for sampling from the posterior distribution. The proposed strategy of using a generative model based on sampling from a model defined in terms of rejection sampling can also be used to construct models for conditional distribution estimation; see Li et. al (2020), who construct a BART-based conditional density estimation model using a model defined through rejection sampling from a baseline density. Our proposed model is applicable for left censored, right censored, and interval censored survival data and our computational algorithms are highly scalable.
to obtain posterior survival prediction. Our simulation studies provide a comprehensive comparison of our proposed model with some existing models for interval-censored survival data. The rest of this paper is organized as follows. In Section 2, we provide a brief review of BART and SBART. In Section 3, we describe our proposed semiparametric model for survival analysis and its extension to censored data, and also provide the data augmentation algorithm used to carry out inference. In Section 4, we present an extensive simulation study to illustrate the performance of the proposed model and compare the results with those obtained from existing methods for survival prediction in interval censored data. In Section 5, we illustrate our methods via analyzing the motivating study of the PSA data. We finally conclude by discussing our key findings in Section 6.

2 A brief review of BART and SBART

The BART framework, proposed by Chipman et al. (2010), is a popular Bayesian ensemble method which combines multiple “weak” decision trees into a single “strong” learner with high predictive accuracy. When the response surface is smooth, as is often the case in practice, BART can be improved theoretically and practically by using the soft BART (SBART) framework introduced by Linero and Yang (2018). SBART makes use of “soft” decision trees, and is capable of adapting to the unknown smoothness level of the response surface. We present here a brief review of BART and SBART.

Consider a nonparametric regression model $Y = f_0(x) + \epsilon$ where $x$ is a $p$-dimensional covariate vector, $f_0 : \mathbb{R}^p \to \mathbb{R}$ is an unknown regression function, and $\epsilon \sim N(0, \sigma^2)$ is a random error. BART models the unknown function $f_0(x)$ as a sum of $T$ regression trees given by $f(x) = \sum_{t=1}^T g(x; \tau_t, \mathcal{M}_t)$, where $\tau_t$ denotes the topology and splitting rules of tree $t$ and $\mathcal{M}_t = (\mu_{t1}, \ldots, \mu_{tL_t})$ denotes the set of predictions associated with the $L_t$ terminal nodes of the $t^{th}$ decision tree. Following Chipman et al. (2010), tree $\tau_t$ is assigned a branching process prior with each node at depth $k = 0, 1, 2, \ldots$ being non-terminal with probability $q(k) = \gamma(1 + k)^{-\beta}$, where $\gamma > 0$ and $\beta > 0$ are positive hyperparameters that control the shape of the tree. For every branch node $b$, a splitting rule of the form $[x_j \leq C_b]$ is assigned with $x$ going down left of the tree if the condition is satisfied and right down the tree otherwise. The splitting
Figure 1: Schematic illustrating how to draw from the prior on \((\tau_t, M_t)\). For this tree, we first determine that the root node will be a branch, which occurs with probability \(\gamma\); we then sample the splitting coordinate \(j = 1\) and the cutpoint \(C = 0.5\). This process then iterates; the left child node is set to be a leaf node with probability \(1 - \gamma/2^\beta\), and the right child is made a leaf with probability \(\gamma/2^\beta\). Eventually this process terminates, and we sample a mean parameter \(\mu\) for each leaf node.

variable \(x_j\) is chosen uniformly from all the \(p\) available variables and \(C_b\) is assigned a Uniform prior on the set of the available splitting values. Independent Gaussian priors are designated to the terminal node parameters, with \(\mu_{t\ell} \sim N(0, \sigma_{\mu}^2)\). A schematic showing how the branching process prior generates a sample of a decision tree, and its associated partition, is given in Figure 1.

While BART is highly flexible and capable of capturing complex regression structures, estimates from BART essentially behave as a sum of step function, and hence lack smoothness. Note that the function \(g(x; \tau_t, M_t)\) can be written as the step function \(g(x; \tau_t, M_t) = \sum_{\ell=1}^{L_t} \varphi_{t\ell}(x; \tau_t) \mu_{t\ell}\), where \(\varphi_{t\ell}(x; \tau_t)\) is the indicator that \(x\) is associated to leaf \(\ell\) of \(\tau_t\). Using BART to estimate \(f(x)\) in this fashion would lead to non-smooth estimates, which is not desirable if \(f(x)\) is believed to be smooth. SBART addresses this drawback by smoothing the weights assigned to each leaf, replacing the indicator function with

\[
\varphi_{t\ell}(x; \tau_t) = \prod_{b \in A_t(\ell)} \psi(x_{jb}; C_b, \alpha_b)^{1-R_b} \{1 - \psi(x_{jb}; C_b, \alpha_b)\}^{R_b}
\]

where \(A_t(\ell)\) denotes the collection of ancestor nodes of leaf \(\ell\) and \(R_b\) is the indicator that the path
from the root to \( \ell \) at branch \( b \) goes right. Here, \( \psi(x; c, \alpha) \) is a continuous distribution function of a location-scale family with location \( c \) and scale \( \alpha \); in this paper, we set \( \psi(x; c, \alpha) \) to be the inverse-logit \( [1 + \exp\{- (x - c)/\alpha\}]^{-1} \). The parameter \( C_b \) plays the role of a cutpoint, while \( \alpha \) functions as a bandwidth parameter, with \( \alpha \to 0 \) corresponding to the usual BART model. When the underlying true \( f(x) \) is smooth, we expect that SBART will provide lower variance than BART while introducing negligible bias. Additionally, Linero and Yang (2018) show that SBART priors are capable of automatically detecting an appropriate amount of smoothness to use. In the next section, we describe the specifications of our flexible semiparametric model for survival prediction while utilizing this improved prediction performance of SBART to model underlying regression structures.

3 A semiparametric model for clustered survival data

Let \( T_{ij} \) denote the survival time and \( x_{ij} = (x_{ij1}, \ldots, x_{ijp}) \in \mathbb{R}^p \) be a vector of \( p \) covariates for subject \( j = 1, \ldots, n_i \) in cluster \( i = 1, \ldots, N \). Let \( f_{ij} \) and \( F_{ij} \) be the density and the cumulative distribution function (respectively) of the survival times \( T_{ij} \), conditional on the parameters of the model and the random effects. We denote the associated survival function as \( S_{ij}(t) = 1 - F_{ij}(t) \) and the hazard function as \( \lambda_{ij}(t) = \frac{f_{ij}(t)}{S_{ij}(t)} \). In this section, we propose a flexible semiparametric model for survival prediction which is well-equipped to capture the complex underlying associations among the different variables in the survival studies, while incorporating unobserved heterogeneity in the population due to random cluster effects. We model the conditional hazard function \( \lambda_{ij}(t \mid W_i; x_{ij}) \) of the survival times \( T_{ij} \) given cluster-specific random frailty \( W_i \) as

\[
\lambda_{ij}(t \mid W_i; x_{ij}) = \lambda_0(t) W_i \Phi(l(t, x_{ij})) \tag{1}
\]

where \( \Phi(\cdot) \) is the distribution function of a standard normal random variable and \( \lambda_0(\cdot) \) is a parametric baseline hazard on which the model is centered; note, for example, that if \( \Phi(l(t, x_{ij})) = 0.5 \), then \( \lambda_{ij}(t \mid W_i; x_{ij}) = \lambda_0(t) W_i/2 \), which is proportional to the baseline hazard \( \lambda_0(t) \). The frailty \( W_i \sim \text{Gamma}(\eta, \eta) \) accommodates within-cluster association, and the covariate effects are modeled
in a time-varying nonparametric fashion via an SBART prior on \( l(t, x_{ij}) \). Our nonparametric model for \( l(t, x_{ij}) \) allows non-linear effects and interactions among the covariates \( x_{ij} \) and the survival times \( t \).

The specification that the shape and rate of the frailty distribution are the same is made to ensure that \( E(W_i) = 1 \), which is required for identifiability (Hougaard, 1995). The amount of unknown heterogeneity among clusters (surgeons for the PSA study) due to random cluster effects is quantified by the variance \( \text{Var}(W_i) = \eta^{-1} \) of the frailties, where a small value of \( \eta \) would indicate a large variability among different clusters in the population. The appeal of our model as in equation (1) is that it is semiparametric. Because of the semiparametric nature, we do not get a direct estimate of the covariate effects, such as the hazard ratio in the more parametrically specified Cox model. However, we can still nonparametrically estimate quantities of interest for our clinical collaborators such as the survival curves or median survival times at given values of covariates, and restricted mean survival time and hazard ratios at a pre-specified time point of interest for given covariate values.

With interval censored survival data, we do not observe \( T_{ij} \), but instead, we only record that \( T_{ij} \) is in the interval \((A_{ij}, B_{ij}]\), where \( A_{ij} \leq B_{ij} \) are the two consecutive inspection times for the unit \((i,j)\). We denote the observed interval censored survival data as \( D = \{(x_{ij}, A_{ij}, B_{ij}) : j = 1, \ldots, n_i; i = 1, \ldots, N\} \) where, \( A_{ij} = B_{ij} \) when \( T_{ij} \) is uncensored, and \( B_{ij} = \infty \) when \( T_{ij} \) is right censored at \( A_{ij} \). Under the hazard function model in (1), the likelihood contribution from the unit \((i,j)\), conditional on the unobserved random effect \( W_i \), is

\[
\Pr[T_{ij} \in (A_{ij}, B_{ij}] \mid W_i; x_{ij}] = S_{ij}(A_{ij} \mid W_i; x_{ij}) - S_{ij}(B_{ij} \mid W_i; x_{ij}),
\]

where

\[
S_{ij}(t \mid W_i; x_{ij}) = \exp \left\{ -W_i \int_0^t \lambda_0(s) \Phi(l(s, x_{ij})) \, ds \right\}
\]

is the conditional survival function of \( T_{ij} \) given frailty \( W_i \). Using the conditional independence of the within-cluster survival times given \( W_i \) and across cluster independence of all survival times, the overall likelihood based on all \( N \) clusters is then derived as

\[
\prod_{i=1}^N \int_0^\infty \left\{ \prod_{j=1}^{n_i} \Pr[T_{ij} \in (A_{ij}, B_{ij}] \mid W_i; x_{ij}] \right\} g(W_i \mid \eta) \, dW_i
\]
after integrating out $W_i$ with respect to its Gamma($\eta, \eta$) density denoted by $g(\cdot \mid \eta)$ in (3). To fully specify the hierarchical Bayesian formulation of our model, we specify prior distributions of our model parameters as $p(\eta, \Omega, l, \Psi) \propto p(\eta) \times p(\Omega) \times p(l \mid \Psi) \times p(\Psi)$, where $p(\eta)$ is the marginal prior of the shape (as well as the scale) parameter \( \eta \) of the Gamma($\eta, \eta$) frailty density, $p(\Omega)$ is the prior on the set of unknown parameters $\Omega$ associated with the parametric baseline hazard $\lambda_0(\cdot)$, and $p(l \mid \Psi)$ and $p(\Psi)$ are the priors associated with the SBART model and its hyperparameters.

In all of our examples, we use a default prior for $\Psi = (\sigma, \mu, \gamma, \beta, r)$ which takes $\sigma = \frac{3}{(k \sqrt{m})}$, $(\gamma, \beta) = (0.95, 2)$, and $r = 10$ where $\alpha_t \sim \text{Gamma}(1, r)$ in the SBART prior, with the same bandwidth $\alpha_t$ being used for all branches within a single tree. We use a Gamma($a, b$) prior for $\eta$, with $a, b > 0$ carefully chosen to reflect our prior opinion about the extent to which the cluster effects $W_i$ can affect the underlying hazard. By default we set $k = 2$.

We fit this model using Markov chain Monte Carlo; the primary challenge in implementing the model (3) with the model specified above is computational, as even evaluating (3) requires numerically evaluating integrals of the form $\int_0^T \lambda_0(s) \Phi(l((s, x)) \, ds$. As such, it is difficult to construct efficient Markov chain Monte Carlo algorithms for sampling from the posterior distribution by working directly with (3). We address this by extending the method of Adams et. al (2009) and Fernandez et. al (2016) to augment the $T_{ij}$’s by viewing them as the first “accepted” point of a thinned Poisson process; this will allow us to obtain simple updates for the distributions for all of the model parameters. We elaborate on the implementation of this data augmentation (DA) scheme for uncensored survival times in Section 3.1 and extend it to left-censored, right-censored, and interval-censored survival times in Section 3.2.

3.1 Data augmentation scheme for no-censoring

From the conditional nonparametric hazard function in (1) and the corresponding survival function (2), it is apparent that the evaluation of the likelihood contribution

$$L_{ij} = W_i \lambda_0(T_{ij}) \Phi(l(T_{ij}, x_{ij})) \exp \left[ - \int_0^{T_{ij}} W_i \lambda_0(s) \Phi(l(s, x_{ij})) \, ds \right] \, ds$$

(4)
for each uncensored $T_{ij}$ case given $W_i$ requires integrating a time-dependent function $\lambda_{ij}(s \mid W_i; x_{ij}) = \lambda_0(s) W_i \Phi(l(s, x_{ij}))$; this involves a nonparametrically modeled function $l(s, x_{ij})$, which varies by the subjects $(i, j)$. Having this time-varying $l(s, x_{ij})$ inside the integral in (4) also prevents us from applying the usual Bayesian backfitting algorithm of Chipman et. al (2010) to update $l(s, x_{ij})$ given the rest of the parameters. To address these challenges, we use a data augmentation procedure, which introduces additional latent variables $\{G_{ijk} \mid k = 1, \ldots, m_{ij}\}$ to ease the posterior computation (that is, by assuring either closed form or standard updates for the conditional posteriors of the parameters). These random latent variables are generated from a Non-homogeneous Poisson Process (NHPP) with intensity $\lambda_0(s) W_i \{1 - \Phi(l(s, x_{ij}))\}$ in the interval $(0, T_{ij})$. This process can be sampled by first simulating a Poisson process with intensity function $\lambda_0(s) W_i$ on the interval $(0, T_{ij})$ and then “thinning” each point with probability $\Phi(l(s, x_{ij}))$. Note that the likelihood of the augmented $G_{ij}$’s simulated via this NHPP is given by

$$
\Pr( \text{events at } G_{ijk} \text{ for } k = 1, \ldots, m_{ij}, \text{ and no other events in } (0, T_{ij}) ) = \prod_{k=1}^{m_{ij}} \lambda_0(G_{ijk}) W_i \{1 - \Phi(l(G_{ijk}, x_{ij}))\} \, dG_{ijk} \times e^{-W_i \int_0^{T_{ij}} \lambda_0(s) \{1 - \Phi(l(s, x_{ij}))\} \, ds}
$$

Combining this likelihood, which is conditional on $T_{ij}$, with the likelihood of $T_{ij}$, gives

$$
\lambda_0(T_{ij}) W_i \Phi(l(T_{ij}, x_{ij})) \times \prod_{k=1}^{m_{ij}} \lambda_0(g_{ijk}) W_i \Phi(Z_{ijk} \mid l(G_{ijk}, x_{ij})) \times e^{-W_i \Lambda_0(T_{ij})},
$$

where $\Lambda_0(t) = \int_0^t \lambda_0(s) \, ds$ denotes the baseline cumulative hazard function of the survival times. This likelihood is greatly simplified because it removes the integral $\int_0^{T_{ij}} \lambda_0(s) \Phi(l(s, x_{ij})) \, ds$ by adding to it $\int_0^{T_{ij}} \lambda_0(s) \{1 - \Phi(l(s, x_{ij}))\} \, ds$, cancelling the $\Phi(l(s, x_{ij}))$ term. While we have phrased this data augmentation directly in terms of simulating $G_{ij}$ from a distribution which simplifies the integral, it is also possible to view this as a traditional data augmentation algorithm by viewing $T_{ij}$ as the first “accepted” point from a “thinned” Poisson process with intensity $\lambda_0(s) W_i$ and acceptance probability $\Phi(l(s, x_{ij}))$, with $G_{ij}$ being the collection of “rejected” points. From this perspective, we are simulating $G_{ij}$ from its full conditional distribution, and (6) gives the joint likelihood of the accepted and the rejected
points (Fernandez et al., 2016).

The augmented likelihood in (6) is still not ideal because the Bayesian backfitting algorithm of Chipman et al. (2010) requires that the likelihood of \( l(t, x) \) takes the form of a semiparametric Gaussian regression \( Z = l(t, x) + \epsilon \) with \( \epsilon \sim N(0, \sigma^2) \); instead, \( l(t, x) \) enters the likelihood through the probit terms \( \Phi(l(T_{ij}, x_{ij})) \) and \( 1 - \Phi(l(G_{ijk}, x_{ij})) \). To accommodate this, we perform another layer of data augmentation using the strategy of Albert and Chib (1993). We introduce truncated normal latent variables \( \{Z_{ijk} ; k = 1, \ldots, m_{ij} + 1\} \) such that

\[
Z_{ijk} \sim \begin{cases} 
N(l(G_{ijk}, x_{ij}), 1)I(-\infty, 0), & \text{if } k = 1, \ldots, m_{ij} \\
N(l(T_{ij}, x_{ij}), 1)I(0, \infty), & \text{if } k = m_{ij} + 1.
\end{cases}
\]

After augmenting the \( Z_{ijk} \)’s to the model, we will use the joint likelihood

\[
\prod_{i=1}^{N} \prod_{j=1}^{n_i} \left\{ \lambda_0(T_{ij}) W_i N(Z_{ij(m_{ij}+1)} | l(T_{ij}, x_{ij}), 1) \times \prod_{k=1}^{m_{ij}} \lambda_0(G_{ijk}) W_i N(Z_{ijk} | l(g_{ijk}, x_{ij}), 1) \times e^{-W_i \Lambda_0(T_{ij})} \right\},
\]

where \( N(x | \mu, \sigma^2) \) denotes the density of a normal distribution with mean \( \mu \) and variance \( \sigma^2 \). This allows us to utilize the continuous outcome SBART model described by Linero and Yang (2018) by treating the \( Z_{ijk} \)’s as Gaussian responses with variance \( \sigma^2 = 1 \). That is, we apply the Bayesian backfitting approach described by Linero and Yang (2018) to the model

\[
Z_{ijk} = l(G_{ijk}, x_{ij}) + \epsilon_{ijk}, \quad \epsilon_{ijk} \sim N(0, 1),
\]

for \( k = 1, \ldots, m_{ij} \), and similarly with \( Z_{ijk} = l(T_{ij}, x_{ij}) + \epsilon_{ijk} \) for \( k = m_{ij} + 1 \).

In addition to updating the function \( l(t, x_{ij}) \) using this data augmentation approach, we must also update the frailties \( W_i \), the parameter of the frailty density \( \eta \), the parameters \( \Omega \) of the baseline hazard \( \lambda_0(\cdot) \), and the hyperparameters \( \Psi \) of the SBART model. For the Gamma(\( \eta, \eta \)) distributed frailties \( W_i \), the likelihood is proportional to \( W_i^{n_i + \sum_j m_{ij}} e^{-W_i \sum_j \Lambda_0(T_{ij})} \) and the corresponding conjugate conditional posterior is Gamma(\( \eta + n_i + \sum_j m_{ij}, \eta + \sum_j \Lambda_0(T_{ij}) \)) where \( n_i \) is the size of the \( i^{th} \) cluster. For the
remaining parameters, we use slice sampling (Neal, 2003).

In summary, our data augmentation scheme is based on the following hierarchical specification of the model, where each line is conditioned on all of the lines above it and all terms within each line are conditionally independent:

\[(\eta, \Psi, \Omega) \sim p(\eta) p(\Psi) p(\Omega)\]
\[l \sim \text{SBART}(\Psi)\]
\[W_i \sim \text{Gamma}(\eta, \eta)\]

Data: \[T_{ij} \sim \lambda_{ij}(t \mid x_{ij}, l, W_i, \Omega) \exp \left\{- \int_0^t \lambda_{ij}(s \mid x_{ij}, l, W_i, \Omega) \, ds \right\}\]
\[
\{G_{ijk} : k = 1, \ldots, m_{ij}\} \sim \text{NHPP}\{\lambda_0(t) W_i (1 - \Phi(l(t, x_{ij}))\text{ for } t \in (0, T_{ij})\}
\]

The steps of the data augmentation algorithm are summarized in Algorithm 1, which also shows how to sample from the NHPP distribution for \(G_{ij}\).

While Algorithm 1 provides the steps of inference and parameter updates with clustered and uncensored survival times \(T_{ij}\), it does not account for the possibility of censoring. In the next sub-section, we discuss the extension of our model for clustered and (left, right or interval) censored survival times.

3.2 Augmenting \(T_{ij}\) for interval censoring

We now consider the case where \(T_{ij}\) is either right or interval censored. Suppose first that \(T_{ij}\) is censored at \(A_{ij}\), so that we observe the event \([T_{ij} \geq A_{ij}]\). Assuming that the censoring mechanism is non-informative (Kalbfleisch and Prentice, 2002) the targeted likelihood contribution of the event \([T_{ij} \geq A_{ij}]\) is \(L_{ij}^* = \exp \left[ - \int_{A_{ij}}^{A_{ij}} \lambda_0(s) W_i \Phi(l(s, x_{ij})) \, ds \right]\). If we augment \(G_{ij}\) as before from the NHPP with intensity \(\lambda_0(s) W_i \{1 - \Phi(l(s, x_{ij}))\}\) then the corresponding augmented data likelihood contribution is not given by...
Algorithm 1: Inference algorithm with clustered and uncensored survival times $T_{ij}$.

**Input:** Observed survival times $T_{ij}$, and initiated values of $\Omega$ (baseline hazard parameter), $l$ (SBART), $\Psi$ (parameters of leaf $l$), $W_i$ (frailty variables) and $\eta$ (shape parameter of the frailty density)

1 for $iteration = 1 : S$ do
2   for $i = 1 : n$ do
3     for $j = 1 : n_i$ do
4       $q_{ij} \sim$ Poisson$(1; \Lambda_0(T_{ij})W_i)$
5       $C_{ij} \sim$ Uniform$(q_{ij}; 0, \Lambda_0(T_{ij})W_i)$
6       $\tilde{G}_{ij} = \Lambda_0^{-1}(\frac{C_{ij}}{W_i})$
7       $U_{ij} \sim$ Uniform$(q_{ij}; 0, 1)$
8       $G_{ij} = \{\tilde{G}_{ij} : U_{ij} \leq 1 - \Phi(l(\tilde{G}_{ij}, x_{ij}))\}$
9       $= \{G_{ij1}, \ldots, G_{ijm_{ij}}\}$
10      $Z_{ijk} \sim \left\{ \begin{array}{ll}
                N(l(G_{ijk}, x_{ij}), 1)I(-\infty, 0), & \text{if } k = 1, \ldots, m_{ij}, \\
                N(l(T_{ij}, x_{ij}), 1)I(0, \infty), & \text{if } k = m_{ij} + 1.
        \end{array} \right.$
11   Update $\Omega$ by slice sampling
12   Update $l$ using the Bayesian backfitting algorithm of Linero and Yang (2018)
13   Update $\Psi$ by slice sampling
14   Update $\eta$ by slice sampling
15   Update $W_i : i = 1, \ldots, n$ by sampling $W_i \sim $ Gamma$(\eta + n_i + \sum_j m_{ij}, \eta + \sum_j \Lambda_0(T_{ij}))$

(6), but instead by

$$L_{ij}^* \times \Pr[\text{“thinned” events at } G_{ij}; \text{ no other “thinned” events in } (0, A_{ij})]$$

$$= \prod_{k=1}^{m_{ij}} \{\lambda_0(G_{ijk}) W_i (1 - \Phi(l(G_{ijk}, x_{ij}))) dG_{ijk}\} \times e^{-W_i \Lambda_0(A_{ij})}. \quad (7)$$

Hence, we can apply the same data augmentation algorithm as before, where the censored observations contribute (7) to the likelihood. To remove the probit terms from the likelihood, we now only simulate $Z_{ijk} \sim N(l(G_{ijk}, x_{ij}), 1)I(-\infty, 0)$ and do not simulate a latent variable for $k = m_{ij} + 1$. For the right-censored setting, let $Y_{ij} = T_{ij}$ if $T_{ij}$ is observed and $A_{ij}$ otherwise. Then the resulting likelihood after performing both layers of data augmentation is

$$\prod_{i=1}^{N} \prod_{j=1}^{n_i} \{\lambda_0(Y_{ij}) W_i N(Z_{ij(m_{ij}+1)} \mid l(Y_{ij}, x_{ij}), 1)\}^{I(Y_{ij}=T_{ij})} \times \prod_{k=1}^{m_{ij}} \lambda_0(G_{ijk}) W_i N(Z_{ijk} \mid l(G_{ijk}, x_{ij}), 1) \times e^{-W_i \Lambda_0(Y_{ij})}.$$
Algorithm 2: Imputation of the survival time for subject $j$ in cluster $i$ with interval censored observation $(A_{ij}, B_{ij}]$

1. set $m^*_ij = 0$
2. while $m^*_ij = 0$
   3. $q^*_ij \sim \text{Poisson}(1; W_i(\Lambda_0(B_{ij}) - \Lambda_0(A_{ij})))I(q^*_ij > 0)$
   4. $C^*_ij \sim \text{Uniform}(q^*_ij; \Lambda_0(A_{ij})W_i, \Lambda_0(B_{ij})W_i)$
   5. $\tilde{G}_{ij} = \Lambda_0^{-1}(C^*_ij/W_i)$
   6. $U^*_ij \sim \text{Uniform}(q^*_ij; 0, 1)$
   7. $G^*_ij = \{ \tilde{G}_{ij} : U^*_ij \leq \Phi(l(\tilde{G}_{ij}, x_{ij})) \} = \{ G^*_{ij1}, \ldots, G^*_{ijm^*_ij} \}$
   8. Impute $T^*_ij$ as $t^*_ij = \min\{ v : v \in G^*_ij \}$

We address interval censoring between $(A_{ij}, B_{ij}]$ by augmenting the true survival time $T_{ij}$; this also addresses left-censoring by setting $A_{ij} = 0$. After augmenting survival time $T_{ij}$, we augment $G_{ij}$ using the same approach as for when $T_{ij}$ is observed. The augmented uncensored survival time $T_{ij}$ can be generated as the smallest event time of a non-homogeneous Poisson process with intensity $\lambda_0(t)W_i\Phi(l(t, x_{ij}))$ on the interval $(A_{ij}, B_{ij}]$ conditional on there being at least one event. An algorithm for augmenting $T_{ij}$ is given by Algorithm 2. The time $T_{ij}$ is sampled by first running a Poisson process with intensity $\lambda_0(t)W_i$ on $(A_{ij}, B_{ij}]$ and then accepting each point $u$ with probability $\Phi(l(u, x_{ij}))$; this process is then repeated until we have at least one acceptance. To make the algorithm more efficient, we condition the initial draw from $\lambda_0(t)W_i$ on $(A_{ij}, B_{ij}]$ to have at least one point. It is important to note here, that the imputation step, as described in Algorithm 2, has to be repeated at the beginning of each iteration, for each subject in the dataset, with left-censored or interval censored survival times.

The algorithms discussed in this section are computationally fast. For example, in our simulation study in section 4 with clustered interval censored survival data (under setting D) with 10 clusters and fixed cluster size 10, the algorithms took 0.16 seconds for each iteration. Similarly, for the PSA data analysis example in Section 5 with 597 total observations and 9 clusters, the algorithm took only 0.22 seconds for each iteration (all computations were performed on a laptop with Intel(R) core i7 processor and 8GB RAM).
4 Simulation Study

In this section, we illustrate the applicability of our proposed semiparametric model for survival prediction in situations when the regression relationships between the survival times and the covariates are non-linear and complex. We compare the performance of our model with some of the existing survival regression models with readily available computational packages under 4 different simulation settings:

1. Simulation A: Survival times are independent and uncensored.
2. Simulation B: Survival times are clustered, but uncensored.
3. Simulation C: Survival times are independent, but interval-censored.
4. Simulation D: Survival times are both clustered as well as interval-censored (thus mimicking the motivating post-surgery PSA recurrence study).

For each of the above simulation settings, we generate $M = 20$ replicates of training datasets, each with $n = 100$ subjects, with a subject-specific 5-dimensional covariate vector $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5)$ drawn from a unit hyper-cube. We first describe the simulation model we use to generate independent and uncensored survival times (for Setting A) and then proceed to describe the extension of this data generation scheme to simulate clustered or/and interval-censored survival times (for Settings B, C and D).

**Data generation scheme:** We use the common test function

$$f_0(\mathbf{x}) = 10 \sin(\pi x_1 x_2) + 20(x_3 - 0.5)^2 + 10x_4 + 5x_5$$

that includes non-linearity and interaction effects among five covariates ($x_1, \ldots, x_5$). The function $f_0$, proposed initially by Friedman (1993), has non-linear dependence on the first three variables $x_1$, $x_2$ and $x_3$, linear dependence on $x_4$ and $x_5$, and incorporates a non-linear interaction between $x_1$ and $x_2$. For the $i^{th}$ subject under simulation A, independent survival times $T_i$ are generated from a Gamma distribution with shape parameter $\lambda_i = f_0(\mathbf{x}_i)$ and rate parameter = 6. The observed independent survival data under
setting A is \( \{x_i, T_i : i = 1, \ldots, n\} \). Predicted survival probabilities are evaluated at a grid of 10 time points, for each of \( n^* = 100 \) independent subjects in a test dataset generated in the same fashion as the training data. Under simulation setting B, each of our \( M = 20 \) replicated training datasets consists of \( N = 10 \) clusters, with fixed cluster size \( n_i = 10 \). We simulate a cluster specific random effect \( W_i \sim \text{Uniform}(0, 0.2) \) and simulate the survival time for the \((i, j)^{th}\) subject as \( T_{ij} \sim \text{Gamma}(\lambda_{ij}, 6) \), where \( \lambda_{ij} = f_0(x_{ij}) + W_i \).

Under simulation setting B, we observe \( \{x_{ij}, T_{ij} : i = 1, \ldots, N, j = 1, \ldots n_i\} \).

From the independent survival times \( T_i \) (generated as in setting A), we obtain interval censored survival times \( (A_i, B_i) \) (for Simulation C) as follows:

- Generate \( K_i \sim \text{Poisson}(T_i) \)
- Set \( A_i = I(K_i = 0) + V_i^{\frac{1}{K_i}} \times T_i \times I(K_i > 0) \), where \( V_i \sim \text{Uniform}(0, 1) \) and \( I(\cdot) \) is an indicator function.
- Set \( B_i = T_i + R_i \), where \( R_i \sim \text{Exponential}(1) \).

This ensures that the censoring mechanism is non-informative. Thus, each replicate of the simulated interval censored survival dataset under setting C is \( \{x_i, A_i, B_i : i = 1, \ldots, n\} \). Finally, clustered and interval censored survival times \( \{(A_{ij}, B_{ij}) : i = 1, \cdots N, j = 1, \cdots n_i\} \) (for simulation D) are obtained following the same interval censoring mechanism as above, except now, the censoring is introduced after simulating the clustered survival times \( T_{ij} \) (as was obtained for simulation setting B).

**Evaluation of model parameters:** The proposed semiparametric model for survival prediction is fitted to the simulated data in each setting, using a constant baseline hazard \( \lambda_0(t) = \Omega \), that is, assuming that the baseline distribution of the survival times is Exponential with rate \( \Omega \). We assign \( \Omega \) a conjugate and relatively non-informative Gamma prior with the shape and the rate hyper-parameters estimated from the data. For analyzing clustered survival times (as in simulation settings B and D), the cluster-specific random effects \( W_i \) are assumed to follow a Gamma distribution with equal shape and rate parameter \( \eta \). Note that the amount of unobserved heterogeneity in the population due to the random cluster effect is
quantified by the variance $\eta^{-1}$ of the frailty $W_i$, where a smaller value of $\eta$ indicates a larger cluster effect on the hazard function. However, it is reasonable to believe that the effect of the frailties on the estimated hazard function will likely be within 25%. This is ensured by assigning $\eta$ a Gamma(4, 0.01) prior, which allows a probability of less than 0.5% for the frailties to influence the hazard function by more than 25%. The SBART component of our model $(l)$ uses a default prior described by Linero and Yang (2018) with 50 trees; we find that this default performs reasonably for the survival setting.

We compare our proposed SBART-based semiparametric model for survival prediction with parametric Accelerated Failure Time models, Cox’s proportional hazards model, random survival forests, and a Bayesian semiparametric proportional hazards model. The parametric Accelerated Failure Time models have been fitted using Weibull distributions for the log-survival times, and the Bayesian semiparametric proportional hazards model (Henschel et al, 2009) (as implemented by SpBayesSurv package in R) uses the transformed Bernstein Polynomial for fitting the baseline hazard functions and independently distributed Gaussian frailties to model the within cluster association for the clustered survival data (for simulations B and D). All Bayesian models were fitted using 2500 burn-in and 2500 sampling iterations. Monte Carlo approximation of the root mean squared error of survival prediction of the $j = 1, 2, \ldots, M = 20$ replicate is obtained as

$$RMSE_j = \sqrt{\frac{\sum_{i=1}^{n^*} \sum_{g=1}^{10} \{S(t_g | x_i) - \hat{S}(t_g | x_i)\}^2}{n^* \times 10}},$$

where $S(t_g | x_i)$ and $\hat{S}(t_g | x_i)$ are respectively the true and the predicted survival probabilities at time point $t_g$ for the $i^{th}$ subject of the test-dataset, having covariate vector $x_i$. For the Bayesian procedures, $\hat{S}(t_g | x_i)$ is taken to be the posterior mean of $S(t_g | x_i)$. Performances of the different methods are compared on the basis of the average root mean squared error, obtained from the 20 replicated simulations and the results are reported in Table 1.

As seen from Table 1, among the methods considered, our proposed model performs the best in predicting survival functions in terms of the average root mean squared error. It has also been shown that our model is easily implementable with clustered and/or interval-censored survival data. It is worth men-
Table 1: Simulation results based on 20 replicates of data comparing Monte Carlo estimates of average Root Mean Squared Error (RMSE) obtained from fitting the parametric accelerated failure time (AFT) model with a Weibull distribution for the log survival times, a random survival forest, Cox’s proportional hazards (PH) model, the proposed semiparametric survival model based on SBART while assuming Gamma frailty and a constant baseline hazard function and a Bayesian semiparametric PH model with Gaussian frailties, and transformed Bernard polynomials for the baseline hazard.

| Methods                                      | Simulation A   | Simulation B   | Simulation C   | Simulation D   |
|----------------------------------------------|---------------|---------------|---------------|---------------|
| (independent, uncensored)                    | 0.7785        | 0.8793        | 0.4366        | –             |
| (independent, interval-censored)             | 0.1798        | –             | –             | –             |
| (clustered, uncensored)                      | 0.1621        | –             | 0.1313        | –             |
| (clustered, interval-censored)               | 0.1038        | 0.1106        | 0.1063        | 0.0944        |
| Semiparametric survival model with SBART     | 0.1403        | 0.1229        | 0.1418        | 0.1211        |
| Bayesian semiparametric PH                   |               |               |               |               |

5 Application: Prostate Surgery Study

We demonstrate the practical utility of our proposed model by analyzing a medical follow-up study to estimate the survival function of the time to recurrence of prostate specific antigen (PSA) among 597 prostate cancer patients who have undergone prostate removal surgeries. PSA level in the blood, immediately following surgery, is 0.0 ng/ml; time to PSA recurrence is defined as the time after surgery when the PSA level in the blood exceeds 0.2 ng/ml. Since continuous monitoring of PSA is not feasible, and the level of PSA in the blood can only determined via blood tests (typically every 3 to 6 months after surgery), the exact time to PSA recurrence is often interval-censored between consecutive post-surgery visits to the clinic. The main analysis goal of the study is to compare the survival function of
the time to PSA recurrence between two surgery techniques (Robotic = 1, RRP = 0) as well as five possible confounders (baseline characteristics): (i) age at surgery (continuous, range 41–77); (ii) number of positive cores (continuous, range 0-17); (iii) Gleason score regarding how the cancer cells are arranged in the prostate (0 = less aggressive, 1 = more aggressive cancers); (iv) surgical margin (0 = negative, 1 = positive); and (v) pT stage (0 = has not spread, 1 = spread). Nine different surgeons (clusters) were included in the study with an average of 66 patients being treated by each surgeon. Of the 597 patients, only 4 (0.67%) had exact recurrence times, 131 (21.9%) were interval-censored, and 462 (77.3%) were right censored. The median age of the patients at the time of surgery was 64 years, with the median number of positive cores being 3. Figure 2 shows the estimated survival curves of times to recurrence of PSA for a patient who had a “more aggressive” prostate cancer (Gleason score = 1) with 3 positive cores and had undergone a prostate removal surgery at 64 years of age. As observed from the picture, the estimated survival curve is the steepest declining when a patient with a positive surgical margin (margin = 1), whose cancer had already spread (pT stage = 1) undergoes a robotic surgery (technique = 1). The survival probabilities improve only marginally when the patient with similar covariates (surgical margin = 1, pT stage = 1) undergoes a non-robotic RRP surgery (technique = 0) instead of a robotic one. A similar pattern with respect to the effect of surgery technique is observed for a patient with all other possible combinations of surgical margin and pT stage. However, there is a strong evidence that both the surgical margin and the pT stage cause a more significant change in the survival probability curve with the probabilities dropping at a faster rate when surgical margin is positive versus negative (margin = 1 versus 0) and when the cancer had spread versus not spread (pT stage = 1 versus 0).

A possible alternative approach to analyze the effect of surgery technique and other covariates on the time to PSA recurrence is to observe the difference in restricted mean survival time caused by varying the covariate values. Restricted mean survival time (RMST) at a pre-specified time point of interest, $\tau$ is defined as $\text{RMST}(\tau) = E[\min(T, \tau)] = \int_0^\tau S(u) \, du$, where $T$ is a non-negative random variable representing the time to event of a particular individual and $S(\cdot)$ is the associated survival function. Inference based on RMST has recently gained popularity, especially due to its ability to summarize survival profiles with non-proportional hazards. Figure 3 shows the differences in RMST to PSA recurrence due to surgery
Figure 2: Estimated survival curves for time to PSA recurrence for a subject who had “more aggressive” prostate cancer (Gleason score = 1) with 3 positive cores and had undergone a prostate removal surgery at 64 years of age. Covariates shown in the legend correspond to different combinations of surgical technique (Robotic or RRP), Surgical margin (positive (Pos.) or negative (Neg.)) and pT stage (Spread or Not spread).

techniques (non robotic RRP - Robotic), surgical margin (negative - positive), and pT stage (not spread - spread) for a patient who had a “more aggressive” prostate cancer (Gleason score = 1) with 3 positive cores and had undergone a prostate removal surgery at 64 years of age. As is evident, the difference in RMST caused due to the surgery technique is always estimated to be less than 3 months. For example, the increase in estimated RMST caused due to non-robotic over a robotic surgery for a patient with positive surgical margin and cancer that had already spread was only around 0.5 months after 54 months from the date of the prostate removal surgery. However, the difference in RMST due to a negative surgical margin over a positive one for a patient undergoing RRP surgery with pT stage = 0 is approximately 5.5 months after around 4.5 years from surgery. Thus all these observations suggest that although there is lack of evidence to belief that surgery technique has a strong impact on time to PSA recurrence, surgical margin and pT stage play a much stronger role in determining the time to PSA recurrence among prostate cancer patients. It should be noted that, for the sake of brevity, here we present the estimated survival functions for only certain specific covariate combinations, however, similar analysis and detailed interpretations can
Figure 3: Difference in Restricted mean survival time (RMST) (measured in months) for time to PSA recurrence due to surgery techniques (RRP - Robotic), surgical margin (negative - positive), and pT stage (not spread - spread) (from left to right) for a patient who had a “more aggressive” prostate cancer (gleason score = 1) with 3 positive cores and had undergone a prostate removal surgery at 64 years of age.

be obtained for all other covariates of interest.

6 Concluding remarks

In this article, we have introduced a robust and flexible semiparametric model for clustered, interval-censored survival data under the BART framework. This was accomplished by modeling the hazard function as a product of a parametric baseline hazard and a nonparametric component that uses SBART to incorporate unknown interactions among the survival times with the different covariates. Besides being applicable for clustered as well as interval-censored survival data, simulation results validate that our model also attains excellent accuracy in survival prediction, while also requiring minor changes to the usual Bayesian backfitting algorithm used to fit other BART models. Code for fitting the SBART interval-censored survival model with clustering will be made available on the authors’ websites. Applicability of the proposed model has been demonstrated via analysis of the motivating post-surgery PSA recurrence study.
An interesting aspect of our methodology is its adaptability to high-dimensional survival studies involving a large number of covariates and complex underlying associations. Although this paper focuses only on the use of SBART to nonparametrically model the deviations of the hazard function from the baseline hazard, our approach can also be extended to allow for ultra-high dimensional predictors when the function \( l(t, x_{ij}) \) is sparse using the sparsity-inducing Dirichlet prior introduced by Linero (2018), as well as allowing for the penalization of groups of predictors simultaneously (Du and Linero, 2019) in a similar fashion to the group Lasso. This approach might be particularly useful when the primary concern of the study is variable selection, and might provide a new direction for future research in survival prediction.

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