A semiparametric probit model for case 2 interval-censored failure time data

Xiaoyan Lin and Lianming Wang

Interval-censored data occur naturally in many fields and the main feature is that the failure time of interest is not observed exactly, but is known to fall within some interval. In this paper, we propose a semiparametric probit model for analyzing case 2 interval-censored data as an alternative to the existing semiparametric models in the literature. Specifically, we propose to approximate the unknown nonparametric nondecreasing function in the probit model with a linear combination of monotone splines, leading to only a finite number of parameters to estimate. Both the maximum likelihood and the Bayesian estimation methods are proposed. For each method, regression parameters and the baseline survival function are estimated jointly. The proposed methods make no assumptions about the observation process and can be applicable to any interval-censored data with easy implementation. The methods are evaluated by simulation studies and are illustrated by two real-life interval-censored data applications. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: Bayesian analysis; interval-censored data; maximum likelihood method; monotone spline; probit model; semiparametric regression

1. Introduction

Interval-censored failure time data commonly arise in many fields such as medical follow-up studies. The main feature of interval-censored data is that the failure time of interest is not observed exactly, but is known to fall within some interval \([1, 2]\). A well-known example in the literature is the breast cancer data discussed in Finkelstein and Wolfe \([3]\), in which the event of interest is the occurrence of breast retraction among early breast cancer patients. Another example is the HIV data set studied in Kroner \([4]\) and Sun \([2]\), where the failure time of interest is the time to HIV-1 infection.

Let \(T_i\) denote the failure time of interest and \(\mathbf{x}_i\), a \(p \times 1\) covariate vector for subject \(i\). Throughout this paper, we assume that \(T_i \sim F(\cdot | \mathbf{x}_i)\). In interval-censored data, \(T_i\) is not observed but falls within an observed interval \((L_i, R_i]\), where \(L_i\) and \(R_i\) are the two closest observation times (including 0 and \(\infty\)) that cover the failure time \(T_i\). To explain the data structure further, suppose that subject \(i\) undergoes an observational process \(\{O_{i1}, \ldots, O_{ik_i}\}\), and the status of failure event is examined only at the observation times. If the failure event for subject \(i\) has already occurred at the first observation time \(O_{i1}\), then \(T_i\) is left-censored and the observed interval is \((0, O_{i1}]\); if the failure event has not occurred at the last observation time \(O_{ik_i}\), then \(T_i\) is right-censored and the observed interval is \((O_{ik_i}, \infty]\); otherwise, \(T_i\) is interval-censored and the observed interval is formed by the two adjacent observation times containing \(T_i\). A data set with all subjects being either left-censored or right-censored is referred to as current status data or case 1 interval-censored data, which usually arises in cross-sectional studies. In this paper, we consider general interval-censored data or case 2 interval-censored data, which is a mixture of left, interval, and right-censored observations. By assuming that subjects are independent, the conditional likelihood given the observed intervals and covariates is then

\[
L = \prod_{i=1}^{n} [F(R_i | \mathbf{x}_i) - F(L_i | \mathbf{x}_i)].
\]  

This likelihood is also a simplified version of the full likelihood under the assumption that the observational process is independent of the failure time given covariates \([2]\). This likelihood is appealing to use since it does not require any assumptions of the observational process. When the conditional independence assumption does not hold, using (1) is still valid but may lose some efficiency compared with the methods based on the full likelihood. However, the full likelihood requires many additional assumptions on the observational process and on the dependence structure between the failure time and the observational process. We refer to Sun \([2]\) for more discussion on the likelihood of interval-censored data.
Semiparametric regression models are popular when dealing with interval-censored data due to their flexibility in modeling the baseline survival function nonparametrically, usually required by the complexity of real-life data. Available semiparametric regression models for interval-censored data in the literature include the proportional hazards (PH) model [5–10], the proportional odds (PO) model [6, 11–13], the additive hazards (AH) model [14–16], the accelerated failure time (AFT) model [17–21], and the linear transformation (LT) model [22, 23]. All the references listed above are from a frequentist’s perspective. On the other hand, the Bayesian methods for interval-censored data are relatively limited. Among others, Sinha et al. [24] studied the PH model; Hanson and Johnson [25] and Komarek and Lesaffre [26] studied the AFT model using a mixture of Dirichlet processes and a normal mixture, respectively.

The research interests in regression analysis are to estimate regression coefficients and the baseline survival function. However, estimating the baseline survival or hazard function is difficult for interval-censored data and theoretical justification is not easy for any semiparametric model due to the complexity of the data structure and the number of parameters being on the order of the sample size. The existing approaches are usually computationally expensive and many of them rely on restrictive assumptions on the observational process. For example, Zeng et al. [14] and Zhu et al. [15] have assumed that there are only two observation times for each subject and that they are independent of the failure time given the covariates.

There are a few methods that allow to estimate the regression parameters directly without estimating the baseline survival function for analyzing case 2 interval-censored data. Under the PH model, Satten [7] proposed a marginal likelihood approach, Goggins et al. [8] developed a Monte Carlo EM algorithm, and Satten et al. [9] proposed estimating equations, all based on the possible rankings of failure times consistent to the observed data. Although these methods are appealing when the primary interest is to estimate the regression parameters, they are computationally expensive due to the involvement of sampling or imputing a large number of possible rankings before maximizing the marginal likelihoods or solving the estimating equations. Recently, Wang et al. [16] proposed an estimating equation approach under the AH model for the failure time. Their approach is easy to implement and does not require estimating any baseline hazard function; however, their approach relies on strict assumptions that all the subjects have the same number of observation times, and that these observation times can be modeled as recurrent events with Cox-type hazard functions.

Motivated by these difficulties and challenges, we propose a semiparametric probit model, which can serve as an alternative to the PH, PO, AH, and AFT models, and develop two approaches, from both the frequentist and the Bayesian perspectives, for analyzing case 2 interval-censored data. The proposed approaches have the following advantages. First, they can be applied to any interval-censored data since they are developed based on the likelihood (1) and require no assumptions about the observational process. Second, they produce smooth estimates of the baseline survival function together with the estimates of regression parameters. Third, they are easy to implement.

The proposed semiparametric probit model specifies the cumulative distribution function (CDF) in the following form:

\[ F(t|x) = \Phi(z(t) + x^T\beta), \quad \forall t \in (0, \infty), \] (2)

where \( \Phi \) is the CDF of a standard normal random variable, \( \beta \) is a \( p \times 1 \) regression coefficient vector denoting the covariate effects, and \( z(t) \) is an unspecified nondecreasing function with \( z(0) = -\infty \) and \( z(\infty) = \infty \). The baseline CDF is \( F_0 = \Phi(z(0)) \) under model (2), and thus \( z \) can be regarded as the transformed baseline CDF with probit link. The regression coefficient \( \beta_j \), the \( j \)th element of \( \beta \), can be interpreted as the increase in the transformed CDF attributable to a unit increase in the \( j \)th covariate.

The proposed model (2) actually falls in the class of semiparametric LT models,

\[ z(T_i) = -x_i^T\beta + \epsilon_i, \]

where the \( \epsilon_i \)'s are iid random errors [22, 23, 27–30]. By taking the distribution of \( \epsilon_i \) to be the standard normal in the above LT model, we obtain the semiparametric probit model (2). One can also obtain the PH and PO models by taking the distribution of \( \epsilon_i \) to be the extreme value distribution and the standard logistic distribution, respectively [22, 23, 27–30]. If \( z \) is taken to be the log function, but with unknown distribution of \( \epsilon_i \), one then obtains the semiparametric AFT model.

Although the proposed probit model falls within the class of LT models, the proposed approaches are different from the existing approaches based on the LT models for analyzing interval-censored data. As a matter of fact, there are only a few approaches available for interval-censored data although many approaches have been developed for right-censored data using the LT models [27, 29, 30]. Ma and Kosorok [28] studied partly LT models for current status data. For case 2 interval-censored data, Younes and Lachin [22] proposed to model the baseline hazard function with B-splines, and Zhang et al. [23] proposed an estimating equation approach that is limited to the case of categorical covariates. The approaches proposed in this paper are easier to implement than the approach of Younes and Lachin [22] and allow both categorical and continuous covariates. Here we focus on the semiparametric probit model because the normal random errors are the most commonly used errors in practice and it is not hard to generalize the proposed methods to other LT models.

The remainder of this paper is as follows. In Section 2, we propose to model the unknown nondecreasing function \( z \) with monotone splines, based on which we develop two estimation methods from the frequentist and the Bayesian perspectives, respectively. Section 3 presents some simulation results of the proposed methods and Section 4 provides two real-life applications. Some discussion is given in Section 5.
2. Proposed methods

2.1. Modeling \( \alpha \) with monotone splines

We consider a common case of interval-censored data where the observation times are continuous and propose to model the unknown nondecreasing function \( \alpha(t) \) in the semiparametric probit model with monotone splines \cite{31},

\[
x(t) = \sum_{l=0}^{k} \gamma_l b_l(t),
\]

where \( b_0(t) = 1 \) for any \( t \) and \( \{ b_l \}_{l=1}^{k} \) are \( l \) (integrated) spline basis functions, each of which is nondecreasing from 0 to 1, and \( \{ \gamma_l \}_{l=1}^{k} \) are taken to be nonnegative values for \( l \geq 1 \) to ensure that \( \alpha \) is nondecreasing. Two components are essential in specifying \( l \) spline basis functions: the knots and the degree. The placement of the knots determines the shape, and the degree determines the smoothness of the \( l \) splines. The \( l \) spline basis functions are totally determined after the knots and the degree are specified \cite{31}. The number of spline basis functions \( k \) equals the number \( m \) of interior knots plus the degree \( d \) of the splines. We refer one to Ramsay \cite{31} for more details about \( l \) spline basis functions.

The expression in (3) is very flexible as it can approximate any nondecreasing continuous function by appropriately choosing the knots and the degree in specifying the \( l \) spline basis function. The choice of the degree often depends on the specific data set and is determined by the investigators. The number of knots also depends on the data. In general, the more knots chosen, the greater the flexibility of the splines functions. However, Ramsay \cite{31} also noted ‘it is not usually necessary in statistical environment to use large numbers of knots’ and recommended to take small numbers of knots in regression. This was also suggested by Rosenberg \cite{32} in modeling the hazard function with B splines for survival data. Potentially, one may allow an environment to use large numbers of knots’ and recommended to take small numbers of knots in regression. This was also suggested by Rosenberg \cite{32} in modeling the hazard function with B splines for survival data. Potential, one may allow an environment to use large numbers of knots’ and recommended to take small numbers of knots in regression.

With the above specification of prior distributions, we develop an efficient Gibbs sampler based on the augmented likelihood (3).

2.2. Bayesian method

In this subsection, we propose a Bayesian method for analyzing case 2 interval-censored data. In general, there are several advantages of using the Bayesian methods. First, the flexible Bayesian hierarchical model structure allows one to work with normal latent variables suggesting that using 10 to 30 equally spaced knots provides sufficient flexibility while not taking too much computation time in using the estimation methods presented below.

We first rewrite (1) in the following equivalent form:

\[
L = \prod_{i=1}^{n} F(R_i|x_i)^{h_1} \left[ F(R_i|x_i) - F(L_i|x_i) \right]^{h_2} \left[ 1 - F(L_i|x_i) \right]^{h_3},
\]

where \( \delta_{11}, \delta_{12}, \) and \( \delta_{13} \) are censoring indicator variables for subject \( i \) denoting left, interval, and right censoring, respectively, subject to the constraint \( \delta_{11} + \delta_{12} + \delta_{13} = 1 \). To facilitate Bayesian computation, we consider a data augmentation by introducing normal latent variables

\[
z_i \sim N(\alpha(t_i) + x_i' \beta, 1),
\]

where \( t_i = R_i \{ \delta_{11} = 1 \} + L_i \{ \delta_{11} = 0 \} \). Then the augmented likelihood function can be written as

\[
L(\beta, \alpha) = \prod_{i=1}^{n} N(z_i; \alpha(t_i) + x_i' \beta, 1) \{ 1(\delta_{11} > 0) \}^{h_1} \{ 1(\delta_{11} = 0, \delta_{12} < 0) \}^{h_2} \{ 1(\delta_{11} = 0, \delta_{13} < 0) \}^{h_3}.
\]

One obtains the likelihood (4) after integrating out all the \( z_i \) in (5).

To complete the Bayesian approach, we assign priors for all of the parameters so that they provide flexible modeling while also allowing for efficient posterior computation. We assign a multivariate normal \( N(\beta_0, \Sigma_0) \) prior for the regression coefficients \( \beta \) and a normal prior \( N(\gamma_0, \Sigma_0) \) for the unconstrained \( \gamma_0 \). We adopt independent exponential priors \( Exp(\eta) \) for all \( \{ \gamma_l \}_{l=1}^{k} \). An exponential prior can shrink small coefficients to zero, serving to penalize the nonzero spline coefficients and thus resulting in basis function selection. To allow for more flexibility, we assign a \( \mathcal{U}(a_{\eta}, b_{\eta}) \) prior for \( \eta \).

With the above specification of prior distributions, we develop an efficient Gibbs sampler based on the augmented likelihood (5). With all the parameters being sampled initially from their priors, the Gibbs sampler proceeds with the following steps at each
iteration:
1. Sample latent variables $z_i$ for $i=1, \ldots, n$.
   (a) If $\delta_{i1} = 1$, sample $z_i$ from $N(x(t_i) + x_i'\beta_1, 1)\{z_i > 0\}$.
   (b) If $\delta_{i2} = 1$, sample $z_i$ from $N(x(t_i) + x_i'\beta_1, 1)\{z_i < 0\}$.
   (c) If $\delta_{i3} = 1$, sample $z_i$ from $N(x(t_i) + x_i'\beta_1, 1)\{z_i = 0\}$.
2. Sample $\gamma_0$ from $N(E_0, W_0^{-1})$, where $W_0 = v_0 + n$ and
   \[ E_0 = W_0^{-1}\left[v_0 m_0 + \sum_{i=1}^{n} \left(z_i - \sum_{l=1}^{k} \gamma_l b_l(t_i) - x_i'\beta\right)\right]. \]
3. Sample $\gamma_l$'s for $l=1, \ldots, k$. For each $l \geq 1$, let $W_l = \sum_{i=1}^{n} b_i^2(t_i)$.
   (a) If $W_l = 0$, sample $\gamma_l$ from the prior $\text{Exp}(\eta)$.
   (b) If $W_l > 0$, sample $\gamma_l$ from $N(E_l, W_l^{-1})\{\gamma_l > 0\}$, where
   \[ E_l = W_l^{-1}\left[\sum_{i=1}^{n} b_i(t_i) \left(z_i - \gamma_0 - \sum_{l' \neq l} \gamma_{l'} b_{l'}(t_i) - x_i'\beta\right)\right]. \]
   \[ d_l^* = \max(c_l^*, 0) \quad \text{and} \quad c_l^* = \max_{h \neq k=1} \left[\frac{-z_i - \sum_{l' \neq l} \gamma_{l'} (b_l(R_i) - b_{l'}(L_i))}{b_l(R_i) - b_{l'}(L_i)}\right]. \]
4. Sample $\beta$ from $N(\tilde{\beta}, \Sigma)$, where $\Sigma = (\Sigma_0^{-1} + \sum_{i=1}^{n} x_i x_i')^{-1}$ and
   \[ \tilde{\beta} = \Sigma \left[\Sigma_0^{-1} \beta_0 + \sum_{i=1}^{n} (z_i - x(t_i))x_i\right]. \]
5. Sample $\eta$ from $\mathcal{G}(a_{\eta} + k, b_{\eta} + \sum_{i=1}^{n} \gamma_i)$.

Note that Step 3 is somewhat complicated since one needs to take into account the constraints $\gamma_l \geq 0$ and $z(t_i) - z_i(R_i) \leq z_i$ for all subjects being interval-censored ($\delta_{i2} = 1$). The above Gibbs sampler is easy to implement since all the full conditional distributions are in standard form.

2.3. Maximum likelihood method
Maximum likelihood method can be naturally applied under the specification of (1), (2), and (3) since there are only a finite number $(1 + k + p)$ of parameters to estimate. Denote $\theta = (\gamma', \beta')'$, where $\gamma = (\gamma_0, \ldots, \gamma_k)'$ are the coefficients of the $1$ splines. The MLE $\hat{\theta}$ can be obtained by maximizing the log of the likelihood function in (1) over a constrained parameter space. This can be done by using an optimization tool in the existing statistical software, for example, the built-in function ‘fmincon’ in Matlab. The variance–covariance matrix of $\hat{\theta}$ can be computed via the inverse observed information matrix, $I^{-1}(\hat{\theta})$, which is derived from the second derivatives of the log-likelihood. However, these second derivatives are complicated even though they have closed form. An alternative way is to numerically approximate the observed information matrix by
\[ I(s, \theta) \approx -n^{-1} h_n^{-2} \left(\log l(\hat{\theta} + h_n \hat{\xi}_s) - \log l(\hat{\theta} + h_n \hat{\xi}_d) - \log l(\hat{\theta} - h_n \hat{\xi}_s) + \log l(\hat{\theta} - h_n \hat{\xi}_d)\right), \]
where $\hat{\xi}_s$ is a $(1 + k + p)$-dimensional vector with the $s$th element equal to $1$ and all other elements equal to $0$, $h_n$ is a tuning constant with order of $n^{-1/2}$, and $\log l$ is the log likelihood function. This method of approximation was also used by Zeng et al. [14] among others.

An alternative way to find the MLE of $\theta$ is to apply a Newton–Raphson method for the unconstrained parameters $(\gamma_0', \xi', \beta')'$, where $\xi = (\xi_1, \ldots, \xi_k)'$ and $\xi_l = \log(\gamma_l)$ for $l = 1, \ldots, k$. An advantage of this method is that one can obtain MLEs as well as their variance estimates directly. However, one needs to calculate the first and the second derivatives of log likelihood, which can be complicated.

3. Simulation studies
Simulation studies are conducted to evaluate the proposed methods. The failure time $T_i$ is generated from $\Phi(x(t_i) + x_1 \beta_1 + x_2 \beta_2)$, where $x_1$ is generated from a standard normal distribution, and $x_2$ is generated from a Bernoulli distribution with success probability 0.5. The true $x(t)$ is taken to be $x(t) = -3 + 4t$ or $x(t) = \log(t)$, $\beta_1 = 1$ or $0$, and $\beta_2 = 1$, $0$, or $-1$, resulting in 12 simulation setups. We allow each subject to have a random number of observations, determined by 1 plus a Poisson random variable with
mean 2. The observation times are produced by generating the gap times between adjacent observation times from independent exponential distributions with mean 1. The observed interval for each subject is determined by the two closest observations (including 0 or ∞) that cover the true failure time. For each setup, 500 independent data sets are generated, each with a sample size 100.

For each generated data set, we take equally spaced knots within the minimum and maximum of the observation times that formed the observed intervals. The distance between two adjacent knots is equal to \( \frac{1}{2} \) or \( \frac{1}{4} \) of the size 100.

First, we apply the proposed methods to the breast cancer data [3] since this data set is the most widely used interval-censored data in the literature. The data came from a retrospective study for radiation therapy in Boston between 1976 and 1980.

### 4. Two real-life applications

#### 4.1. Breast cancer data

First, we apply the proposed methods to the breast cancer data [3] since this data set is the most widely used interval-censored data in the literature. The data came from a retrospective study for radiation therapy in Boston between 1976 and 1980.
Table II. Simulation results with $x(t) = \log(t)$, based on 500 data sets.

<table>
<thead>
<tr>
<th>True $\beta_1$</th>
<th>Est. $\hat{\beta}_1$</th>
<th>ESE</th>
<th>SSD</th>
<th>CP95</th>
<th>True $\beta_2$</th>
<th>Est. $\hat{\beta}_2$</th>
<th>ESE</th>
<th>SSD</th>
<th>CP95</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_1 = 1$</td>
<td>$\hat{\beta}_1$</td>
<td>1.0758</td>
<td>0.1894</td>
<td>0.2081</td>
<td>0.940</td>
<td>$\hat{\beta}_2$</td>
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<td>$\hat{\beta}_2$</td>
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</tr>
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</table>

Table III. Mean square errors of the estimates of $\beta_1$, $\beta_2$, and $F_0$, based on 500 data sets.

<table>
<thead>
<tr>
<th>True $x(t) = -3 + 4t$</th>
<th>Bayesian method</th>
<th>Likelihood method</th>
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</thead>
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<td>$x(t) = \log(t)$</td>
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<td>MSE ($\hat{\beta}_1$)</td>
<td>MSE ($\hat{\beta}_1$)</td>
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<tr>
<td>$(\beta_1, \beta_2) = (0, 1)$</td>
<td>MSE ($\hat{\beta}_1$)</td>
<td>MSE ($\hat{\beta}_1$)</td>
</tr>
<tr>
<td>$(\beta_1, \beta_2) = (1, 0)$</td>
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<td>MSE ($\hat{\beta}_1$)</td>
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<tr>
<td>$(\beta_1, \beta_2) = (0, 0)$</td>
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<td>MSE ($\hat{\beta}_1$)</td>
</tr>
<tr>
<td>$(\beta_1, \beta_2) = (1, -1)$</td>
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<td>MSE ($\hat{\beta}_1$)</td>
</tr>
<tr>
<td>$(\beta_1, \beta_2) = (0, -1)$</td>
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<td>$x(t) = \log(t)$</td>
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<td>MSE ($\hat{\beta}_1$)</td>
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<td>$(\beta_1, \beta_2) = (1, 0)$</td>
<td>MSE ($\hat{\beta}_1$)</td>
<td>MSE ($\hat{\beta}_1$)</td>
</tr>
<tr>
<td>$(\beta_1, \beta_2) = (0, 0)$</td>
<td>MSE ($\hat{\beta}_1$)</td>
<td>MSE ($\hat{\beta}_1$)</td>
</tr>
<tr>
<td>$(\beta_1, \beta_2) = (1, -1)$</td>
<td>MSE ($\hat{\beta}_1$)</td>
<td>MSE ($\hat{\beta}_1$)</td>
</tr>
<tr>
<td>$(\beta_1, \beta_2) = (0, -1)$</td>
<td>MSE ($\hat{\beta}_1$)</td>
<td>MSE ($\hat{\beta}_1$)</td>
</tr>
</tbody>
</table>

One objective of this study was to detect whether chemotherapy changes the rate of deterioration of the cosmetic state. There were 94 early breast cancer patients in two treatment groups, with 46 women receiving radiation therapy alone and the other 48 receiving radiation therapy together with adjuvant chemotherapy. In this study, patients were examined periodically and actual examination times differed from patient to patient since some of them missed their visits. The failure time event was defined as breast retraction, which only has interval-censored data available \([2, 3, 5]\).

We define $x_i = 1$ if subject $i$ received radiation therapy only and 0 if subject $i$ received combined therapy. We tried various numbers $m$ of equally spaced interior knots in \((3, 50)\) and degrees $d$ of the monotone splines to investigate their influence on the performance of the proposed methods. Table IV displays the point estimates of the regression parameter as well as the corresponding 95 per cent intervals for each combination of $m$ and $d$. The results show that estimation is overall robust in terms of providing similar point estimates and close 95 per cent intervals obtained from both methods. The likelihood method gives slightly larger point estimates than the Bayesian method in all cases. In addition, there is a tendency that the results are getting less significant as the number of knots $m$ increases. For example, several of the 95 per cent intervals contain 0 under both methods when $m=15$. These results suggest that the difference between the transformed risks of breast contraction for the two groups may not be significant. This discovery is different from those in Finkelstein [5] and Cai and Betensky [10] under the PH model and in Shen [13] under the PO model, all of which reported a highly significant difference between the two groups. This inconsistency may be explained as follows. Each of the probit, PH, and PO models implies that the survival functions for the two groups do not cross each other. However, the nonparametric maximum likelihood estimates of the survival functions, computed
Table IV. Results of the breast cancer data analysis: point estimates and 95 per cent interval estimates of the regression parameter for different numbers \((m)\) of equally spaced knots and degrees \((d)\) in the monotone spline specification.

<table>
<thead>
<tr>
<th></th>
<th>(d=4)</th>
<th>(d=3)</th>
<th>(d=2)</th>
<th>(d=1)</th>
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<tr>
<td>Bayes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(m=5)</td>
<td>0.4774</td>
<td>0.4529</td>
<td>0.4523</td>
<td>0.4584</td>
</tr>
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<td></td>
<td>(0.0556, 0.9162)</td>
<td>(0.0316, 0.9051)</td>
<td>(0.0248, 0.9026)</td>
<td>(0.0431, 0.8825)</td>
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<tr>
<td>(m=8)</td>
<td>0.4649</td>
<td>0.4647</td>
<td>0.4568</td>
<td>0.4473</td>
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<tr>
<td></td>
<td>(0.0450, 0.9229)</td>
<td>(0.0256, 0.9078)</td>
<td>(0.0033, 0.9183)</td>
<td>(0.0146, 0.8826)</td>
</tr>
<tr>
<td>(m=10)</td>
<td>0.4663</td>
<td>0.4641</td>
<td>0.4521</td>
<td>0.4547</td>
</tr>
<tr>
<td></td>
<td>(0.0340, 0.9209)</td>
<td>(0.0259, 0.9302)</td>
<td>(0.0190, 0.8947)</td>
<td>(0.0126, 0.8985)</td>
</tr>
<tr>
<td>(m=15)</td>
<td>0.4568</td>
<td>0.4616</td>
<td>0.4357</td>
<td>0.4454</td>
</tr>
<tr>
<td></td>
<td>(−0.0012, 0.9393)</td>
<td>(0.0001, 0.8962)</td>
<td>(−0.0053, 0.8889)</td>
<td>(0.0059, 0.9082)</td>
</tr>
<tr>
<td>Likelihood</td>
<td></td>
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<tr>
<td>(m=5)</td>
<td>0.4986</td>
<td>0.5041</td>
<td>0.5096</td>
<td>0.5159</td>
</tr>
<tr>
<td></td>
<td>(0.0370, 0.9603)</td>
<td>(0.0466, 0.9616)</td>
<td>(0.0542, 0.9651)</td>
<td>(0.0609, 0.9708)</td>
</tr>
<tr>
<td>(m=8)</td>
<td>0.4855</td>
<td>0.4946</td>
<td>0.4884</td>
<td>0.5097</td>
</tr>
<tr>
<td></td>
<td>(0.0148, 0.9562)</td>
<td>(0.0223, 0.9669)</td>
<td>(0.0186, 0.9582)</td>
<td>(0.0538, 0.9655)</td>
</tr>
<tr>
<td>(m=10)</td>
<td>0.4841</td>
<td>0.4794</td>
<td>0.4812</td>
<td>0.4804</td>
</tr>
<tr>
<td></td>
<td>(0.0052, 0.9630)</td>
<td>(0.0044, 0.9544)</td>
<td>(0.0051, 0.9573)</td>
<td>(0.0070, 0.9538)</td>
</tr>
<tr>
<td>(m=15)</td>
<td>0.4734</td>
<td>0.4795</td>
<td>0.4716</td>
<td>0.4695</td>
</tr>
<tr>
<td></td>
<td>(−0.0073, 0.9541)</td>
<td>(−0.0022, 0.9611)</td>
<td>(−0.0087, 0.9519)</td>
<td>(−0.0105, 0.9496)</td>
</tr>
</tbody>
</table>

Figure 1. Nonparametric estimates of survival functions for both treatment groups in the breast cancer example. The Bayes and the MLE estimates are obtained under the stratified probit models with monotone spline formulation.

by the Turnbull algorithm [35], show the opposite, as seen in Figure 1. It actually indicates that none of these three models is appropriate for analyzing the breast cancer data.

We instead analyze the breast cancer data by fitting the probit model (2) without covariates separately for each treatment group. The proposed methods yield nonparametric Bayesian and maximum likelihood estimates of the survival functions based only on the monotone spline formulation (3). For comparison, Figure 1 also plots the stratified MLE and Bayesian survival estimates for each group when \(m=8\) and \(d=4\). The stratified survival estimates are close to the corresponding Turnbull estimates, indicating good performance of our proposed methods.

4.2. Hemophilia data

A multicenter prospective study was conducted in the 1980’s to investigate HIV-1 infection rate among people with hemophilia [4]. The patients were at risk of HIV-1 infection from blood products made from donors’ plasma. In this study, only case 2 interval-censored data were observed for patients’ HIV-1 infection times. The patients were categorized into one of four groups according to the average annual dose of the blood products they received: high-, median-, low-, or no-dose group. More details about this study can be found in Kroner et al. [4]. Following Sun [2], we focus on the low-dose group (132 patients) and no-dose group (236 patients) only. We define \(x_i=1\) if patient \(i\) is in the low-dose group and 0 otherwise.
Table V lists the point estimates of the regression parameter as well as the corresponding 95 per cent intervals for different numbers \( m \) of equally spaced interior knots within \((2, 60)\) and different degrees \( d \) of splines. From Table V, the results obtained from both methods are robust for different values of \( m \) and \( d \). The likelihood method seems to be slightly more robust than the Bayesian method. All the results in Table V suggest that the patients in the low-dose group have significantly higher HIV-1 infection rate than those in the control group. This conclusion is consistent with the findings in Sun [2] and Cai and Betensky [10] using the PH model.

Figure 2 shows the Turnbull estimates and the estimated survival functions from the maximum likelihood and the Bayesian methods when \( m = 10 \) and \( d = 4 \). The 95 per cent pointwise credible intervals for the Bayesian estimates are also presented. As seen in Figure 2, our estimates are close to the Turnbull estimates, indicating that the probit model assumption is reasonable.

5. Discussion

The probit model has been widely used in generalized linear (mixed) models, but it is rarely seen in the field of survival analysis. In this paper, we propose a semiparametric probit model for analyzing case 2 interval-censored data. One key point is to adopt linear combinations of monotone splines to approximate the unknown nondecreasing function \( x \) in the probit model, leading to a finite number of parameters to estimate, while still providing adequate flexibility. Based on this, we develop a Bayesian approach and a maximum likelihood approach for estimation. Both two approaches are easy to implement and are applicable to any case 2 interval-censored data set. Our simulation results and two data analyses also suggest that both methods work well in practical situations.

In the paper, we specify a moderate size of equally spaced knots, which seems to be adequate for model fitting. In the case that a large number of knots are needed, for example, when the sample size is very large, one can use a penalized maximum
likelyhood method, such as in Cai and Betensky [10] and Rosenberg [32]. The Bayesian method proposed in this paper can still be applied without any adjustment because the adopted shrinkage prior for the monotone spline coefficients can automatically select important spline bases by forcing the coefficients of unnecessary bases to be zero.

The idea of modeling nondecreasing functions with monotone splines can also be applied to other semiparametric models in the literature. For example, (3) can be used to model the log baseline odds function in the PO model and the log baseline cumulative hazard function in the PH model, which is much simpler than the modeling in Shen [13] and Cai and Betensky [10] for the PO and the PH, respectively. The proposed maximum likelihood or a penalized likelihood method can then be applied directly to such models.

There is a strong connection between the probit model and the logistic model due to the fact that a random variable following a logistic distribution can be generated from a normal variable with a random variance following a specific distribution [36, 37]. Based on this connection, Holmes and Held [38] and Wang and Dunson [39] adopted a normal latent variable approach in logistic regression for complete data and in the semiparametric PO model for current status data, respectively. Following the same idea, the proposed Bayesian algorithm can be modified to analyze case 2 interval-censored data with the PO model by adding one extra sampling step for the random variances.

Acknowledgements

The authors thank Joshua M. Tebbs for suggestions on improving the original manuscript and thank the editor, an associate editor, and two reviewers for their helpful comments.

References


