Cox Regression Analysis of Dependent Interval-Censored Failure Time Data

Ling Ma^{a,*}, Tao Hu^b, Jianguo Sun^a

^a*Department of Statistics, University of Missouri, Columbia, MO, United States*

^b*School of Mathematical Sciences and BCMIS, Capital Normal University, Beijing, China*

Abstract

Many procedures have been proposed for regression analysis of interval-censored failure time data arising from the Cox or proportional hazards model. However, most of these existing methods only apply to the situation where the censoring mechanism generating censoring intervals is independent of the failure time of interest, and it is well-known that sometimes this may not be true in practice. To address this issue, a new approach that allows the dependence between the censoring mechanism and the failure time is proposed. More specifically, a situation where the dependence is through the length of censoring intervals is considered as it is often the case in follow-up studies. The asymptotic properties of the proposed estimators are established and the numerical studies are conducted for the assessment of the finite sample properties of the estimators.

Keywords: Copula model; Cox model; Dependent interval-censoring; Efficient semiparametric estimation

1. Introduction

This paper discusses regression analysis of interval-censored failure time data arising from the Cox or proportional hazards model. By interval-censored data, we mean that instead of being observed exactly, the failure time of interest is observed only to belong to an interval, commonly denoted by $(L, R]$ or $L < T \leq R$ (Chen et al., 2012; Finkelstein, 1986; Huang, 1996; Sun, 2006). That is, the occurrence of the failure event of interest is known only to be within the interval $(L, R]$. Examples of the areas that often produce such data include health or medical follow-up studies such

*Corresponding author

Email address: mlbegood@gmail.com (Ling Ma)

as clinical trials as well as social sciences. In addition, it is easy to see that the interval-censored data include right-censored data, whose analysis has been extensively discussed in the literature,
10 as a special case (Kalbfleisch and Prentice, 2002).

The analysis of interval-censored failure time data has been attracting more and more attention recently and especially, many methods have been developed for their regression analysis under various regression models including the proportional hazards model. For example, a pioneering work was given by Finkelstein (1986), which discussed the fitting of the Cox model to the data,
15 and for the same problem, Goggins et al. (1998) and Zhang et al. (2010) developed a Markov chain Monte Carlo EM algorithm and a spline-based maximum likelihood approach, respectively. Also among others, Zhang et al. (2005) proposed an estimating equation procedure for fitting the linear transformation model to interval-censored data. More and relatively complete references on this can be found in Chen et al. (2012) and Sun (2006).

For the analysis of interval-censored failure time data, it is easy to see that in addition to the failure time T of interest, one may need to concern the mechanism that generates L and R also. For this, most of the existing methods assume the noninformative or independent mechanism under which one can carry out the conditional analysis given $L < T \leq R$. On the other hand, it is apparent that this may not be true in some situations. In a clinical trial with the follow-up of both
25 healthy subjects and patients, for example, the patients may tend to pay more clinical visits than the scheduled ones. Several methods have been proposed in the literature for the analysis of dependent interval-censored data. For example, Finkelstein et al. (2002) and Betensky and Finkelstein (2002) considered the one-sample problem related to such data, and Zhang et al. (2007) gave a latent variable-based estimation procedure for regression analysis of dependent interval-censored data
30 from the Cox model. Note that the method in Zhang et al. (2007) used a log-normal frailty to describe the dependence structure and it is apparent that in reality, it may be difficult to check such specific dependence structure. In other words, a more general model or procedure would be clearly needed.

In the following, we will discuss the same problem considered as Zhang et al. (2007) and present
35 a more general, copula model-based approach. More specifically, we will assume that the pair $(L, R]$ is generated from an underline observation process and focus on the case where the dependence between the failure time and the censoring mechanism can be described by the length of censoring intervals. One situation where this can happen is medical follow-up studies where subjects may

pay more or less clinical visits. For the analysis, a maximum likelihood estimation procedure will
 40 be developed with the use of I -spline functions (Ramsay, 1988; Lu et al., 2007). Both the model
 and the method will be described in the next section. In Section 3, some asymptotic properties of
 the proposed estimators are established, including the consistency and asymptotic normality of the
 estimated regression parameters, and the variance estimation is discussed. Some simulation results
 are presented in Section 4 and Section 5 provides an illustrative example. Finally Section 6 contains
 45 some discussion and concluding remarks.

2. Semiparametric Maximum Likelihood Estimation

Consider a failure time study that involves n independent subjects and yields only interval-
 censored failure time data. For subject i , let T_i denote the failure time of interest and Z_i the vector
 of covariates, and suppose that there exists an array of underlying observation times $\mathbf{E}_i = \{E_{i,j} :$
 50 $j = 0, 1, 2, \dots\}$ such that $E_{i,j} < E_{i,j'}$ for any $j < j'$. Define $W_{i,j} = E_{i,j} - E_{i,j-1}, j = 1, 2, \dots$, the
 gap times of the observation process with $E_{i0} = 0$ and assume that given Z_i , the $W_{i,j}$'s follow the
 same distribution. Furthermore assume that T_i may depend on the underlying observation process
 through the gap times and that given Z_i , $\{(T_i, W_{i,j}), j = 1, 2, \dots\}$ follow the same joint distribution.
 In the following, for each i , define $(\tilde{L}_i, \tilde{R}_i]$ to be the random interval among $(0, E_{i,1}]$, $(E_{i,1}, E_{i,2}]$, $\dots$
 55 that contains T_i . Note that the mechanism behind the observation process and censoring intervals
 here is similar to that behind the mixed case k interval-censored data (Shick and Yu, 2000; Sun,
 2006).

In practice such as in medical follow-up studies, there usually exists an administrative censoring
 time ζ_i beyond which the observation process is no longer available. For each i , define $L_i =$
 $\max\{E_{i,j} : E_{i,j} < \min(\zeta_i, T_i), j = 0, 1, 2, \dots\}$ and $R_i = \min\{E_{i,j} : E_{i,j} > L_i, j = 1, 2, \dots\}$. Also,
 define $\delta_i = 1$ if $R_i \leq \zeta_i$ and $\delta_i = 0$ otherwise. Note that when $\delta_i = 0$, R_i is not observed but
 right-censored at ζ_i and T_i is right-censored. For ease of explanation, we define $(\tilde{L}_i, \tilde{R}_i]$ as covering
 interval and $(L_i, R_i]$ as 'observed interval' (even though R_i is not directly observed for right-censored
 subjects). And define $W_i = R_i - L_i$ as the 'observed interval length'. It is easy to see that if $\delta_i = 1$,
 W_i is exactly observed and T_i lies in the observed interval. For subjects with $\delta_i = 0$, note that L_i is
 not necessarily equal to $\tilde{L}_i$ and also $(L_i, R_i]$ may not contain T_i . In fact, since R_i is right-censored
 at ζ_i , we only observe that $T_i > L_i$ and $W_i > \zeta_i - L_i$. An illustrative example for this situation
 with $\delta_i = 0$ is given in Figure 1. Assume that given Z_i and T_i belonging to the censoring interval,

the distribution of T_i depends on the censoring interval only through its length. That is, we have

$$Pr(T_i \leq t \mid L_i < T_i \leq R_i; L_i = l_i, R_i = r_i, Z_i = z_i) = Pr(T_i \leq t \mid l_i < T_i \leq r_i; W_i \equiv r_i - l_i, Z_i = z_i).$$

Then the likelihood function has the form

$$\prod_{i=1}^n \left[Pr(L_i = l_i < T_i \leq R_i = r_i, W_i = w_i) \right]^{\delta_i} \left[Pr(T_i > L_i = l_i, W_i > \zeta_i - l_i) \right]^{1-\delta_i}.$$

Figure 1: An illustrative example of right-censored observations.

Let K denote the joint distribution of T and W given Z . Then it is well-known (Nelsen, 2006) that there exists a copula function $C_\alpha(u, v)$ defined on $I^2 = [0, 1] \times [0, 1]$ such that

$$K(t, w) = C_\alpha(F_T(t), F_W(w)), \quad t \geq 0, \quad w \geq 0.$$

In the above, F_T and F_W denote the marginal distributions of the T and W given Z , respectively, α , usually referred to as the association parameter, represents the relationship between T and W , and $C_\alpha(u, 0) = C_\alpha(0, v) = 0$, $C_\alpha(u, 1) = u$ and $C_\alpha(1, v) = v$. Define $m_\alpha(F_T(t), F_W(w)) = P(T \leq t \mid W = w, Z)$. Then we have

$$m_\alpha(F_T(t), F_W(w)) = \frac{\partial C_\alpha(u, v)}{\partial v} \Big|_{u=F_T(t), v=F_W(w)}.$$

For the covariate effects, we will consider the following marginal Cox hazard models

$$\lambda_T(t|Z_i) = \lambda_1(t) \exp(Z_i' \beta), \quad \lambda_W(w|Z_i) = \lambda_2(w) \exp(Z_i' \gamma),$$

for T_i and W_i given Z_i , respectively. Here $\lambda_1(t)$ and $\lambda_2(w)$ are unknown baseline hazard functions and β and γ denote vectors of regression parameters.

60 It is worth noting that the copula model formulation described above has been commonly used in multivariate failure time data analysis (Hougaard, 2000) as well as the analysis of univariate failure time data in the presence of informative censoring. For example, by using the formulation, Zheng

and Klein (1995) discussed the estimation of a marginal survival function based on right-censored data in the presence of dependent competing risks, and Chen (2010) considered the regression analysis of the same data. In particular, they showed that without prior or extra information, the association parameter α is not identifiable given the copula function. In the following, following these authors, we will assume that both the copula function and α are known and our main goal is to estimate regression parameters β and γ .

For estimation of β and γ , first note that it follows from the models defined above that we have $F_{T_i}(t) = F_T(t|Z_i) = 1 - \exp(-\Lambda_1(t) \exp(Z_i' \beta))$ and $F_{W_i}(w) = F_W(w|Z_i) = 1 - \exp(-\Lambda_2(w) \exp(Z_i' \gamma))$. Define $\theta = (\beta, \gamma, \Lambda_1(t), \Lambda_2(w))$. Hence the likelihood function $L(\theta)$ can be rewritten as

$$L(\theta) = \prod_{i=1}^n \left\{ \left([m_\alpha\{F_{T_i}(r_i), F_{W_i}(w_i)\} - m_\alpha\{F_{T_i}(l_i), F_{W_i}(w_i)\}] f_{W_i}(w_i) \right)^{\delta_i} \times \left(1 - F_{W_i}(\zeta_i - l_i) - F_{T_i}(l_i) + C_\alpha\{F_{T_i}(l_i), F_{W_i}(\zeta_i - l_i)\} \right)^{1-\delta_i} \right\},$$

where $f_{W_i}(w_i) = \lambda_2(w_i) \exp(Z_i' \gamma) \exp\{-\Lambda_2(w_i) \exp(Z_i' \gamma)\}$.

To estimate the regression parameters or θ , it is apparent that a natural approach is to directly maximize the log likelihood function $l(\theta) = \log L(\theta)$. However, it is easy to see that this would not be straightforward as one has to deal with unknown functions Λ_1 and Λ_2 . Instead we propose to approximate the two functions by I -spline functions first and then maximize the resulting sieve maximum likelihood function. Similar approaches have been used by Zhang et al. (2010) and others. More specifically, let $\{I_j(t)\}_{j=1}^{m+k_n}$ denote the I -spline base functions with order m and k_n interior knots, where $k_n = o(n^\nu)$ with $0 < \nu < 0.5$. Define $\varphi = (\Lambda_1, \Lambda_2)$ and

$$\Theta_n = \left\{ \theta_n = (\beta, \gamma, \varphi_n) : \varphi_n = (\Lambda_{1n}, \Lambda_{2n}) \right\} = \mathcal{B} \otimes \mathcal{M}_n^1 \otimes \mathcal{M}_n^2.$$

In the above, $\mathcal{B} = \{(\beta, \gamma \in R^{2p}, \|\beta\| + \|\gamma\| \leq M)\}$,

$$\mathcal{M}_n^1 = \left\{ \Lambda_{1n} : \Lambda_{1n}(t) = \sum_{j=1}^{m+k_n} \xi_j I_{j1}(t), \xi_j \geq 0, j = 1, \dots, m+k_n, t \in [l_t, u_t] \right\},$$

$$\mathcal{M}_n^2 = \left\{ \Lambda_{2n} : \Lambda_{2n}(w) = \sum_{j=1}^{m+k_n} \eta_j I_{j2}(w), \eta_j \geq 0, j = 1, \dots, m+k_n, w \in [l_w, u_w] \right\},$$

where M is a positive constant, $[l_t, u_t]$ and $[l_w, u_w]$ denote the ranges of $\{l_i, r_i, i = 1, 2, \dots, n\}$ and $\{\min(w_i, \zeta_i - l_i), i = 1, 2, \dots, n\}$, respectively. In other words, instead of the original parameter space, we can focus on the space Θ_n when maximizing the log likelihood function $l(\theta)$.

To see the validity of the space Θ_n , for a vector a and a function f , let $\|a\|$ denote the Euclidean norm and $\|f\|_\infty = \sup_t |f(t)|$, the supremum norm. Also for a random variable X with the probability measure P , define $\|f(X)\|_2 = (\int f^2 dP)^{1/2}$, the $L^2(P)$ norm, and

$$d^2(\theta^1, \theta^2) = \|\beta^1 - \beta^2\|^2 + \|\gamma^1 - \gamma^2\|^2 + \|\Lambda_1^1 - \Lambda_1^2\|_2^2 + \|\Lambda_2^1 - \Lambda_2^2\|_2^2,$$

for $\theta^i = (\beta^i, \gamma^i, \Lambda_1^i, \Lambda_2^i)$, $i = 1, 2$. Then it is easy to see that for any $\theta \in \Theta$, there exists a sequence of $\theta_n = (\beta, \gamma, \Lambda_{1n}, \Lambda_{2n}) \in \Theta_n$ such that $d(\theta, \theta_n) \leq c(\|\Lambda_1 - \Lambda_{1n}\|_\infty + \|\Lambda_2 - \Lambda_{2n}\|_\infty) = O(n^{-r\nu})$ for some constant c and $r = m + \eta$, where η is defined in the condition (A4) given in the Appendix. It thus follows from Lemma A1 of Lu et al. (2007) that Θ_n can be used as a sieve space of Θ , and for estimation of θ , we can define the estimator $\hat{\theta} = (\hat{\beta}, \hat{\gamma}, \hat{\Lambda}_{1n}(\cdot), \hat{\Lambda}_{2n}(\cdot))$ as the value of θ that maximizes the log likelihood function $l(\theta)$ over Θ_n . We will establish the asymptotic properties of $\hat{\theta}$ in the next section.

3. Asymptotic Properties

In this section, we establish the asymptotic properties of $\hat{\theta}$. First we give the consistency and the convergence rate of $\hat{\theta}$ and then the asymptotic normality of $\hat{\beta}$ and $\hat{\gamma}$. All limits below are taken as $n \rightarrow \infty$. Let $\theta_0 = (\beta_0, \gamma_0, \Lambda_{10}, \Lambda_{20})$ denote the true value of θ .

Theorem 1. *Suppose that the conditions A1-A4 described in the Appendix hold. Then $\hat{\beta}$ and $\hat{\gamma}$ are strong consistent estimators of β_0 and γ_0 and furthermore, we have $\|\hat{\Lambda}_{1n} - \Lambda_{10}\|_2 \rightarrow 0$ and $\|\hat{\Lambda}_{2n} - \Lambda_{20}\|_2 \rightarrow 0$ almost surely.*

Theorem 2. *Suppose that the conditions A1-A4 described in the Appendix hold. Then we have $\|\hat{\Lambda}_{1n} - \Lambda_{10}\|_2 + \|\hat{\Lambda}_{2n} - \Lambda_{20}\|_2 = O_p(n^{-(1-\nu)/2} + n^{-r\nu})$.*

Theorem 3. *Assume that $r > 2$ and the conditions A1 - A5 described in the Appendix hold. Then we have $n^{1/2}((\hat{\beta} - \beta_0)', (\hat{\gamma} - \gamma_0)')' \rightarrow N(0, \Sigma)$ in distribution and furthermore, $(\hat{\beta}', \hat{\gamma}')'$ is semiparametrically efficient, where Σ is given in the Appendix.*

Note that by approximating the original parameter space by the I -spline function space, we change the original maximization problem to a much easy one over a finite parameter space. The results above says that they are asymptotically equivalent. To implement the estimation procedure above, one needs to choose the order m and the number of knots k_n . The selection of m should

usually be decided based on the smoothness of the true baseline cumulative hazard functions, and in general, either quadratic or cubic spline functions work sufficiently well in practice. For a given problem, a simple method is to try different values of m and k_n and compare the obtained results. To be more objective, an alternative is to apply the Akaike information criterion (AIC) to choose m and k_n that give the smallest AIC and more comments on this are given below. We will sketch the proofs of the theorems above in the Appendix.

For inference, once $\hat{\beta}$ and $\hat{\gamma}$ are determined, it is apparent that one needs to estimate their covariance matrix or Σ . For this, two approaches are commonly used. One is the profile likelihood approach that needs the determination of the profile likelihood of β and γ and then employ the the inverse of the observed information matrix of the profile likelihood. The other approach is to directly employ the inverse of the observed information matrix of the likelihood function $L(\theta)$ by treating Λ_{1n} and Λ_{2n} as finite-dimensional nuisance parameters. It is easy to see that the former may be much more complicated than the latter. More importantly, the latter is straightforward by using the existing procedures such as the function `nlm` in R, which is also used for the determination of $\hat{\theta}$ in the numerical studies below. In addition, the simulation results below suggest that the latter seems to work well for practical situations.

For the implementation of the estimation procedure above, in the numerical studies below, we used the R function `nlm` to the perform optimization. The `nlm` function carries out a minimization of the objective function using a Newton-type algorithm (Dennis and Schnabel, 1996). In the function `nlm`, the line search methods are used to obtain global convergence and under certain proper conditions, the convergence of algorithm can be established (see Theorem 3.6 and Theorem 3.7 in Nocedal and Wright, 2006). The simulation studies indiate that it seems to work well and reasonably fast.

4. A Simulation Study

In this section, we report some results obtained from an extensive simulation study conducted to assess the finite sample properties of the estimation procedure given in the previous sections. In the study, we considered the following three copula models

$$C_\alpha(u, v) = \exp \left\{ -[(-\log u)^\alpha + (-\log v)^\alpha]^{1/\alpha} \right\}, \quad \alpha \geq 1,$$

$$C_\alpha(u, v) = uv + \alpha uv(1-u)(1-v), \quad -1 \leq \alpha \leq 1,$$

and

$$C_\alpha(u, v) = \log_\alpha \left\{ 1 + \frac{(\alpha^u - 1)(\alpha^v - 1)}{\alpha - 1} \right\}, \quad \alpha \geq 0, \alpha \neq 1.$$

120 In the literature, they are usually referred to as Gumbel, FGM and Frank models, respectively. Note that as mentioned above, here the association parameter α represents the correlation between the failure time of interest T and the censoring interval length W . Since the range of α is different for different copula models, we follow the convention of using the Kendall's τ instead. For the three models above, the relationship between α and τ is $\tau = 1 - 1/\alpha$, $\tau = 2\alpha/9$, and $\tau = 1 + 4\rho^{-1}\{D_1(\rho) -$
 125 $1\}$, respectively. Here $\rho = -\log \alpha$ and $D_1(\rho) = \rho^{-1} \int_0^\rho t(e^t - 1)^{-1} dt$.

For the study, we suppose that the covariate Z_i 's are binary variables taking value 0 or 1 with the probability 0.5. For the generation of the observed data, we first generate the failure time T_i with $\Lambda_{10}(t) = t$ and then solve the equation

$$P(W \leq w_i | T_i = t_i, Z_i = z_i) = \frac{\partial C_\alpha(u, v)}{\partial u} \Big|_{u=F_T(t_i), v=F_W(w_i)} = a,$$

for w_i given T_i and a random number a generated from the uniform distribution $U(0, 1)$. Here we took $\Lambda_{20}(w) = 2w$. Given $W_i = w_i$, we define the censoring interval by letting l_i be the largest number in $\{0, w_i, 2w_i, 3w_i, \dots\}$ that is smaller than $\min\{T_i, \zeta_i\}$. If $l_i + w_i \leq \zeta_i$, then $\delta_i = 1$ with $r_i = l_i + w_i$ and otherwise, $\delta_i = 0$. Constant censoring times $\zeta_i = \zeta$ were used for all results. The
 130 results below are based on 1000 replications with the sample size $n = 200$.

Table 1 presents the results on estimation of regression parameters when the copula model is correctly specified. The results include the estimated bias (Bias) given by the average of the estimators minus the true value, the sample standard deviation (SSE) of the estimators, the average of the estimated standard errors (SEE), and the 95% empirical coverage probability (CP). Quadratic
 135 splines with $k_n = 4$ interior knots were used for estimation of both $\Lambda_{10}(t)$ and $\Lambda_{20}(w)$. For $\Lambda_{10}(t)$, the interior knots were taken to be the 0.2, 0.4, 0.6 and 0.8 quantiles of the pooled set of all l_i 's and the observed r_i 's, while for $\Lambda_{20}(w)$, the 0.2, 0.4, 0.6 and 0.8 quantiles of the pooled set of the observed w_i 's and the $(\zeta - l_i)$'s from right-censored subjects were used.

The results suggest that the proposed estimation procedure seems to work well for the situations
 140 considered here. More specifically, the estimator seems to be unbiased and the variance estimation appears to be reasonable. The results also indicate that the normal approximation to the distribution of the estimated regression parameters appears to be appropriate. The Q-Q plots, which are not shown here, suggest the same. Note that in addition to the hazard function used above, we

Table 1: Simulation results on estimation of regression parameters with correctly specified copula models and constant baseline hazard functions.

Under Gumbel copula											
$\tau = 0.2$						$\tau = 0.5$					
	True	Bias	SSE	SEE	CP		True	Bias	SSE	SEE	CP
β	0	-0.008	0.160	0.157	0.950	β	0.2	-0.005	0.155	0.152	0.950
γ	0.2	-0.005	0.160	0.158	0.933	γ	0.2	0.018	0.154	0.151	0.942
Under FGM copula											
$\tau = -0.1$						$\tau = 0.1$					
	True	Bias	SSE	SEE	CP		True	Bias	SSE	SEE	CP
β	0	-0.005	0.160	0.160	0.960	β	0	-0.002	0.165	0.161	0.952
γ	0.2	0.009	0.158	0.157	0.956	γ	0.2	0.003	0.167	0.163	0.953
Under Frank copula											
$\tau = -0.5$						$\tau = 0.5$					
	True	Bias	SSE	SEE	CP		True	Bias	SSE	SEE	CP
β	0.2	-0.006	0.147	0.143	0.948	β	0	-0.015	0.168	0.156	0.937
γ	-0.2	0.011	0.144	0.145	0.952	γ	0.2	-0.015	0.179	0.162	0.933

Table 2: Simulation results on estimation of regression parameters with correctly specified copula models and non-constant baseline hazard functions.

Under Gumbel copula											
$\tau = 0.2$						$\tau = 0.5$					
	True	Bias	SSE	SEE	CP		True	Bias	SSE	SEE	CP
β	0	0.023	0.165	0.163	0.943	β	0.2	-0.000	0.165	0.161	0.947
γ	0.2	-0.002	0.165	0.162	0.951	γ	0.2	0.051	0.142	0.160	0.978
Under FGM copula											
$\tau = -0.1$						$\tau = 0.1$					
	True	Bias	SSE	SEE	CP		True	Bias	SSE	SEE	CP
β	0	-0.005	0.169	0.167	0.949	β	0	0.019	0.173	0.166	0.940
γ	0.2	0.005	0.162	0.163	0.948	γ	0.2	0.016	0.174	0.168	0.938
Under Frank copula											
$\tau = -0.5$						$\tau = 0.5$					
	True	Bias	SSE	SEE	CP		True	Bias	SSE	SEE	CP
β	0.2	0.044	0.171	0.174	0.944	β	0	0.030	0.192	0.179	0.934
γ	-0.2	0.052	0.161	0.186	0.978	γ	0.2	-0.026	0.181	0.191	0.956

also considered the use of other baseline hazard functions for generating failure times. For example, Table 2 presents the estimation results on the regression parameters with $\Lambda_{10}(t) = t^2/4 + t/2$ and $\Lambda_{20}(w) = w^2/2 + w$, and they gave similar conclusions to those in Table 1.

Note that in the estimation procedure proposed above, we have assumed that the copula model is known and of course this may not be true in practice. On this, a question of practical interest is possible model misspecification and we also performed some simulation studies to investigate it. Table 3 presents some results obtained under two situations with constant baseline hazard functions. One is that we generated the data from the Gumbel copula with the relatively strong association, but performed the analysis by assuming that they arose from the Frank copula. The other is to generate the data from the FGM copula with weak association, but carry out the analysis by treating them from the Frank copula. In both cases, for comparison, we also considered

155 the use of the naive approach that ignores the dependent censoring and included the estimation
 results in the table. In addition, to evaluate the proposed AIC-based model selection procedure, we
 calculated the percentages of times when the right model was picked (PRP) among 1000 simulation
 replications and reported them in Table 3. One can see from the upper two panels of Table 3
 that when the true dependence is relatively strong, the analysis with the misspecified copula model
 160 or the naive method seems to yield significant estimation biases of regression parameter β . For
 the estimation of regression parameter γ , the analysis with misspecified copula model seems to
 yield strongly significant estimation bias, while the results with naive analysis seems comparable
 to that using correct copula model. This might be because the interval widths have right-censored
 data with part of the widths exactly observed, thus independent analysis of it does not lose much
 165 information. Please note that our primary interest lies in estimation of β . Thus we consider that
 the analysis with correct model outperforms the naive analysis. In this case with relatively strong
 dependence, the AIC based model selection approach was able to pick up the correct Gumbel copula
 97.0% and 95% of the times for the two parameter settings, relatively, and picked Frank copula for
 the rest times. For the situation where the true dependence is weak, as indicated by the results in
 170 the lower panel of Table 3, the estimators seem to be insensitive to the misspecification of copula
 models and the naive method seems to perform reasonably well as expected. In this case, the AIC
 model selection approach picked up the correct FGM copula 48.9% of the times and the Frank
 copula 51.1% times as expected since all copulas are similar when the association is weak. We also
 considered some other set-ups and obtained similar results.

175 **5. An Illustrative Example**

To illustrate the estimation procedure developed in the previous sections, we apply it to a set
 of interval-censored data analyzed by Zhang et al. (2007) among others. One purpose of the study
 was to investigate the relationship between cytomegalovirus (CMV) shedding and baseline CD4 cell
 counts and in the study, the patients were followed and tested for CMV shedding in their blood and
 180 urine periodically. Since some of the patients missed some of the predetermined visits and returned
 with their blood and/or urine CMV shedding status changed, only interval-censored data were
 observed for the times to CMV shedding. In addition to the observed intervals on CMV shedding
 times, the baseline CD4 cell count was also obtained for each patient.

Table 3: Simulation results on estimation of regression parameters with mis-specified copula model or naive analysis ignoring dependent censoring and constant baseline hazard functions.

Data generated from Gumbel copula with $\tau = 0.5$													
Analysis	using correct copula					using Frank copula				Naive analysis			
	True	Bias	SSE	SEE	CP	Bias	SSE	SEE	CP	Bias	SSE	SEE	CP
β	0.2	-0.005	0.155	0.152	0.950	0.014	0.171	0.160	0.937	-0.026	0.162	0.162	0.954
γ	0.2	0.018	0.154	0.151	0.942	0.038	0.173	0.164	0.936	0.008	0.157	0.161	0.959
PRP=97%													
Data generated from Gumbel copula with $\tau = 0.5$													
Analysis	using correct copula					using Frank copula				Naive analysis			
	True	Bias	SSE	SEE	CP	Bias	SSE	SEE	CP	Bias	SSE	SEE	CP
β	0.5	-0.015	0.160	0.153	0.945	0.038	0.174	0.161	0.922	-0.063	0.164	0.164	0.934
γ	0.5	0.051	0.159	0.153	0.925	0.102	0.176	0.165	0.892	0.031	0.165	0.163	0.946
PRP=95.2%													
Data generated from FGM copula with $\tau = 0.1$													
Analysis	using correct copula					using Frank copula				Naive analysis			
	True	Bias	SSE	SEE	CP	Bias	SSE	SEE	CP	Bias	SSE	SEE	CP
β	0	-0.002	0.165	0.161	0.952	-0.002	0.165	0.161	0.953	-0.008	0.163	0.161	0.954
γ	0.2	0.003	0.167	0.163	0.953	0.003	0.166	0.163	0.954	0.000	0.162	0.161	0.957
PRP=48.9%													

For the analysis, by following Zhang et al. (2007), we will dichotomize the baseline CD4 cell count and define $Z = I(CD4 < 75)$. In the analysis, we set ζ_i to be the largest examination time plus 0.1 and considered the same three copula models and quadratic splines as in the simulation study. First we will consider the time to CMV shedding in urine. For this, we tried several values for the number of knots including $k_n = 2, 3, 4, 5, 6$. For the association parameter τ , we did grid search for each situation as shown in Figure 2. The smallest AIC is given by the estimation under the Gumbel copula model with $k_n = 5$ and $\tau = 0.83$. Table 4 presents the estimation results with $k_n = 5$, under Gumbel, FGM and Frank copulas, and at a number of τ values including the corresponding optimal τ values 0.83, 2/9 and 0.79, respectively. The table includes the estimated treatment effect, $\hat{\beta}$, the estimated effect on the censoring interval length, $\hat{\gamma}$, the estimated standard errors (SEE) and the p -values for testing no treatment effects. One can see from the table that as expected, the results differ depending on the copula model and the association.

Under the Gumbel copula model with $k_n = 5$ and $\tau = 0.83$, we have $\hat{\beta} = 0.64$ with $SEE = 0.18$, corresponding to a p -value of 0.0004 for testing $\beta = 0$. This indicates that the time to CMV shedding in urine for patients with baseline CD4 counts less than 75 seems to be significantly shorter than other patients. This result is consistent with that given by Zhang et al. (2007), which gives $\hat{\beta} = 0.80$ with the estimated standard error of 0.17 and the p -value < 0.0001 . The results in Table 4 also suggest that the patients with baseline CD4 counts less than 75 seem to pay significantly more clinical visits. The AIC selected τ value suggests that there exists some positive association between the time to CMV shedding in urine and the clinical visits. Zhang et al. (2007) concluded no significant association between CMV shedding in urine and visit compliance based on the fact that the estimation of β using their proposed frailty model was close to the estimation of β under the analysis assuming independent censoring (Finkelstein, 1986). But there was no direct quantified justification on the association. Also note that the regression parameters in the latent variables-based approach in Zhang et al. (2007) have different interpretations from those in our copula model based approach or those in Finkelstein (1986). As pointed out by Goethals et al. (2008) the regression parameters from the frailty model have a conditional meaning (conditional on the frailty), while the corresponding marginal hazard function of Zhang et al. (2007) does not have the proportional structure. Thus our conclusion of the relatively strong association between CMV shedding in urine and visit compliance seems more convincing. More discussions can be found in Section 6.

Figure 2: AIC values at a grid of τ values under Gumbel, FGM and Frank copulas.

Table 4: Estimated treatment effects for CMV shedding in urine.

copula	τ	$\hat{\beta}$	SEE	p -value	$\hat{\gamma}$	SEE	p -value	AIC
Gumbel	0	0.89	0.20	< 0.0001	0.57	0.19	0.0033	1119.7980
	0.25	0.96	0.20	< 0.0001	0.67	0.20	0.0006	1019.7581
	0.5	0.89	0.19	< 0.0001	0.65	0.19	0.0006	936.1881
	0.75	0.73	0.18	< 0.0001	0.57	0.18	0.0019	869.8624
	0.83	0.64	0.18	0.0004	0.52	0.18	0.0043	861.0044
FGM	-2/9	0.79	0.23	0.0004	0.43	0.21	0.0421	1242.5600
	-1/9	0.86	0.20	< 0.0001	0.54	0.20	0.0071	1175.5460
	0	0.89	0.20	< 0.0001	0.57	0.19	0.0033	1119.7980
	1/9	0.89	0.20	< 0.0001	0.57	0.19	0.0028	1072.5910
	2/9	0.87	0.20	< 0.0001	0.56	0.19	0.0031	1031.7420
Frank	-0.5	0.61	0.24	0.0115	0.35	0.23	0.1363	1440.8235
	-0.25	0.80	0.21	0.00001	0.51	0.20	0.0127	1250.6426
	0	0.89	0.20	< 0.0001	0.57	0.19	0.0033	1119.7980
	0.25	0.87	0.19	< 0.0001	0.58	0.19	0.0019	1015.2402
	0.5	0.80	0.18	< 0.0001	0.56	0.18	0.0016	926.5547
	0.75	0.69	0.18	0.0001	0.54	0.18	0.0020	864.6551
	0.79	0.66	0.18	0.0003	0.54	0.18	0.0027	862.8108

215 Table 5 gives the analysis results on the CMV shedding time in blood with $k_n = 3$. As above, we also performed the analysis by using different numbers of knots under each of the three copula models and the smallest AIC value is given by the estimation under the Gumbel copula model with $k_n = 3$ and $\tau = 0.93$. For the case, we obtained $\hat{\beta} = 1.11$ with the estimated standard error being 0.42, corresponding to a p -value of 0.0079 for testing $\beta = 0$. In comparison, Zhang et al. (2007) 220 gave $\hat{\beta} = 0.81$ with the standard error of 0.33 and the p -value of 0.014, and both methods suggest some significant effect of the baseline CD4 count on the CMV shedding time. Also the proposed approach indicates that the censoring mechanism seems to be positively related with the CMV shedding in blood.

Note that in the proposed estimation approach, the marginal proportional hazards model is 225 used for both the failure time of interest T and the observation interval length W . To complete the analysis, one may also want to verify these assumptions. For W , since right-censored data are observed, the model check is straightforward and actually we obtained the p -values of 0.064 and 0.495 for CMV shedding in blood and urine, respectively. They suggest that the proportional hazards model seems to be appropriate.

230 6. Discussion and Concluding Remarks

In the preceding sections, an approach has been proposed for regression analysis of interval-censored failure time data when the failure time of interest and the censoring mechanism may be dependent through the length of censoring intervals. As mentioned before, such data occur quite often in medical studies and other investigations although only limited research exists due to the 235 difficulties involved. Also as mentioned above, for the analysis, we have assumed that the copula model and the association parameter are known as they are not identifiable in general without extra information or data. In order to perform the analysis, one way is to try different models and parameter values similarly to a sensitivity analysis. Also as done in Sections 4 and 5, one could apply the AIC for the determination or selection of appropriate copula model and association 240 parameter. The same issue occurs in many other areas too such as in tumorigenicity experiments (Lagakos and Louis, 1988).

In the proposed method, we have employed the copula model approach and I -spline functions. With respect to the former, as pointed above, another commonly used approach for modeling correlated variables is through the use of latent variables, which often requires some complicated

Table 5: Estimated treatment effects for CMV shedding in blood.

copula	τ	$\hat{\beta}$	SEE	p -value	$\hat{\gamma}$	SEE	p -value	AIC
Gumbel	0	1.20	0.42	0.0039	0.77	0.41	0.0637	544.6019
	0.25	1.25	0.43	0.0040	0.82	0.43	0.0555	500.5852
	0.5	1.25	0.44	0.0049	0.88	0.43	0.0428	457.0369
	0.75	1.17	0.43	0.0063	0.92	0.42	0.0295	412.4883
	0.93	1.11	0.42	0.0079	1.00	0.42	0.0160	387.0831
FGM	-2/9	1.11	0.41	0.0062	0.67	0.39	0.0841	625.1859
	-1/9	1.19	0.41	0.0041	0.74	0.41	0.0734	574.0249
	0	1.20	0.42	0.0039	0.77	0.41	0.0637	544.6019
	1/9	1.22	0.42	0.0035	0.79	0.41	0.0567	523.3384
	2/9	1.23	0.42	0.0031	0.81	0.41	0.0499	506.2520
Frank	-0.5	1.17	0.41	0.0041	0.71	0.41	0.0822	726.6607
	-0.25	1.19	0.41	0.0042	0.73	0.41	0.0773	611.5466
	0	1.20	0.42	0.0039	0.77	0.41	0.0637	544.6019
	0.25	1.23	0.42	0.0031	0.82	0.41	0.0455	496.9193
	0.5	1.24	0.41	0.0025	0.89	0.41	0.0283	457.4012
	0.75	1.17	0.39	0.0030	0.91	0.39	0.0178	418.3175
	0.94	1.04	0.36	0.0041	0.92	0.35	0.0085	388.7243

245 computation procedures for parameter estimation. Also the distribution of latent variable is usually
prespecified in these approaches and thus restricts the dependence to a specific structure which
might not be true for certain data sets. Another note on the latent variables-based approach and
our proposed copula-based approach is that, the regression parameter from the latent variable model
has a conditional meaning, whereas that from the copula model refers to the marginal hazard and
250 survival functions. Specifically, using notations of Zhang et al. (2007), given covariate X_i and frailty
 b_i , they assumed that the hazard function for T_i has the form $\lambda_i^{(T)}(t) = \lambda_{t0}(t) \exp\{\beta'_t X_i + b_{1i}\}$. Then
the marginal survival function can be written as $S_i^{(t)}(t) = \int \exp\{-\Lambda_{t0}(t) \exp(\beta'_t X_i + b_{1i})\} f(b_{1i}) db_{1i}$,
where $\Lambda_{t0}(t) = \int_0^t \lambda_{t0}(u) du$ and $f(b_{1i})$ is the density function of b_{1i} . The corresponding marginal
hazard function no longer has the proportional structure as the models studied in this paper. Thus,
255 one should use these approaches accordingly. For the use of I -spline functions, of course, one could
employ other spline or smooth functions. One advantage of the I -spline functions is that they avoid
the order restriction of the spline coefficients compared to some others such as monotone B-spline
functions. In this paper, we have focused on the data arising from the Cox model. It should be
straightforward to develop similar estimation procedures for the data from other semiparametric
260 regression models such as linear transformation models (Zhang et al., 2005). On the other hand,
it may not be easy but would be useful to develop similar estimation procedures for the situation
where both lower and upper bounds of the censoring interval may be related to the failure time of
interest.

Acknowledgements

265 This research was partly supported by the Natural Science Foundation of China (11201317,
11371062) to the second author and a NSF grant to the third author.

Appendix A. Proofs of Theorems 1 – 3

For the proof of Theorems 1 - 3, we need the following regularity conditions.

- (A1) The covariate Z has a bounded support in R^p , where p is the dimension of Z .
- 270 (A2) The copula function $C_\alpha(\cdot, \cdot)$ has bounded first order partial derivatives and $\partial C_\alpha(u, v)/\partial u$
and $\partial C_\alpha(u, v)/\partial v$ are Lipschitz.

(A3) Let $l(\theta, X)$ denote the log likelihood function based on the single observation $X = (\delta, L, R, Z, \zeta)$ as defined in Section 2. For any positive number ϵ , we have that

$$\sup_{d(\theta, \theta_0) > \epsilon} Pl(\theta, X) < Pl(\theta_0, X).$$

(A4) For $k = 1, 2$, the m th derivative of $\Lambda_k(\cdot)$, denoted by $\Lambda_k^{(m)}(\cdot)$, is Holder continuous with exponent η . That is, there exist a positive real value M and some $\eta \in (0, 1]$ such that $|\Lambda_k^{(m)}(t_1) - \Lambda_k^{(m)}(t_2)| \leq M|t_1 - t_2|^\eta$ for all $t_1, t_2 \in (l, u)$, $k = 1, 2$. In the following, we denote $r = m + \eta$.

275 (A5) The matrix $E(S_\vartheta S'_\vartheta)$ is finite and positive definite with $\vartheta = (\beta', \gamma')'$, where S_ϑ is defined in the proof of Theorem 3 below.

These conditions are mild and usually satisfied in practice (Huang and Rossini, 1997; Zhang et al., 2010). In the following proofs of Theorems 1 - 3, the empirical process theory and some techniques commonly used in nonparametric literature will be involved. For ease of exposition, we denote $Pg = \int g(x)dP(x)$ and $P_n g = n^{-1} \sum_{i=1}^n g(X_i)$, the empirical process indexed by function $g(X)$. And we let K, M, M_n, C be generic constants in the following and could vary from place to place.

Proof of Theorem 1: To establish the consistency, we will employ the empirical process theory and need the following two lemmas, whose proofs are given in the Supporting Information to save the space.

Lemma 1 (Calculation of the covering number). Under Conditions (A1) and (A2), the covering number of the class $\mathcal{L}_n = \{l(\theta, X) : \theta \in \Theta_n\}$ satisfies

$$N(\epsilon, \mathcal{L}_n, L_1(P_n)) \leq KM^{2p}M_n^{2(m+k_n)}\epsilon^{-p_m},$$

where $p_m = 2p + 2(m + k_n)$.

Lemma 2 (Uniform convergence). Under Conditions (A1) and (A2), we have

$$\sup_{\theta \in \Theta_n} |P_n l(\theta, X) - Pl(\theta, X)| \rightarrow 0,$$

almost surely.

For the proof, consider the class $\mathcal{L}_n$ and note that according to Lemma 1, the covering number of the class $\mathcal{L}_n$ satisfies

$$N(\epsilon, \mathcal{L}_n, L_1(P_n)) \leq KM^{2p}M_n^{2(m+k_n)}\epsilon^{-p_m},$$

where $p_m = 2p + 2(m + k_n)$. Furthermore, by Lemma 2, we have

$$\sup_{\theta \in \Theta_n} |P_n l(\theta, X) - Pl(\theta, X)| \rightarrow 0, \quad (\text{A.1})$$

almost surely. Let $M(\theta, X) = -l(\theta, X)$, $\zeta_{1n} = \sup_{\theta \in \Theta_n} |P_n M(\theta, X) - PM(\theta, X)|$, $\zeta_{2n} = P_n M(\theta_0, X) - PM(\theta_0, X)$, and denote $K_\epsilon = \{\theta : d(\theta, \theta_0) \geq \epsilon, \theta \in \Theta_n\}$. By (A.1), we have

$$\begin{aligned} \inf_{K_\epsilon} PM(\theta, X) &= \inf_{K_\epsilon} \left\{ PM(\theta, X) - P_n M(\theta, X) + P_n M(\theta, X) \right\} \\ &\leq \zeta_{1n} + \inf_{K_\epsilon} P_n M(\theta, X). \end{aligned} \quad (\text{A.2})$$

If $\hat{\theta}_n \in K_\epsilon$, we can get that

$$\inf_{K_\epsilon} P_n M(\theta, X) = P_n M(\hat{\theta}_n, X) \leq P_n M(\theta_0, X) = \zeta_{2n} + PM(\theta_0, X). \quad (\text{A.3})$$

With condition (A3), we obtain that $\inf_{K_\epsilon} PM(\theta, X) - PM(\theta_0, X) = \delta_\epsilon > 0$. Further analysis by using (A.2) and (A.3) leads to $\inf_{K_\epsilon} PM(\theta, X) \leq \zeta_{1n} + \zeta_{2n} + PM(\theta_0, X) = \zeta_n + PM(\theta_0, X)$ with $\zeta_n = \zeta_{1n} + \zeta_{2n}$. Hence, we have $\zeta_n \geq \delta_\epsilon$ which implies that $\{\hat{\theta}_n \in K_\epsilon\} \subseteq \{\zeta_n \geq \delta_\epsilon\}$. By (A.1) and strong law of large numbers, we have $\zeta_{1n} = o(1)$ almost surely and $\zeta_{2n} = o(1)$ almost surely. Therefore, by $\cup_{k=1}^\infty \cap_{n=k}^\infty \{\hat{\theta}_n \in K_\epsilon\} \subseteq \cup_{k=1}^\infty \cap_{n=k}^\infty \{\zeta_n \geq \delta_\epsilon\}$, we complete the proof.

Proof of Theorem 2

To derive the convergence rate, for any $\eta > 0$, define the class $\mathcal{F}_\eta = \{l(\theta_{n0}, X) - l(\theta, X) : \theta \in \Theta_n, d(\theta, \theta_{n0}) \leq \eta\}$ with $\theta_{n0} = (\beta_0, \gamma_0, \Lambda_{1n0}, \Lambda_{2n0})$. Following the calculation of Shen and Wong (1994, p.597), we can establish that $\log N_{[]}(\varepsilon, \mathcal{F}_\eta, \|\cdot\|_2) \leq CN \log(\eta/\varepsilon)$ with $N = 2(m + k_n)$. Moreover, some algebraic calculations lead to $\|l(\theta_{n0}, X) - l(\theta, X)\|_2^2 \leq C\eta^2$ for any $l(\theta_{n0}, X) - l(\theta, X) \in \mathcal{F}_\eta$.

Therefore, by Lemma 3.4.2 of van der Vaart and Wellner (1996), we can obtain

$$E_P \|n^{1/2}(P_n - P)\|_{\mathcal{F}_\eta} \leq C J_\eta(\varepsilon, \mathcal{F}_\eta, \|\cdot\|_2) \left\{ 1 + \frac{J_\eta(\varepsilon, \mathcal{F}_\eta, \|\cdot\|_2)}{\eta^2 n^{1/2}} \right\}, \quad (\text{A.4})$$

where $J_\eta(\varepsilon, \mathcal{F}_\eta, \|\cdot\|_2) = \int_0^\eta \{1 + \log N_{[]}(\varepsilon, \mathcal{F}_\eta, \|\cdot\|_2)\}^{1/2} d\varepsilon \leq CN^{1/2}\eta$. The right-hand side of (A.4) yields $\phi_n(\eta) = C(N^{1/2}\eta + N/n^{1/2})$. It is easy to see that $\phi_n(\eta)/\eta$ decreases in η , and $r_n^2 \phi_n(1/r_n) = r_n N^{1/2} + r_n^2 N/n^{1/2} < 2n^{1/2}$, where $r_n = N^{-1/2}n^{1/2} = n^{(1-\nu)/2}$ with $0 < \nu < 0.5$. Hence $n^{(1-\nu)/2}d(\hat{\theta}, \theta_{n0}) = O_P(1)$ by Theorem 3.2.5 of van der Vaart and Wellner (1996). This, together with $d(\theta_{n0}, \theta_0) = O_p(n^{-r\nu})$ (Lemma A1 in Lu et al. (2007)), yields that $d(\hat{\theta}, \theta_0) =$

305 $O_p(n^{-(1-\nu)/2} + n^{-r\nu})$. The choice of $\nu = 1/(1+2r)$ yields the rate of convergence of $d(\hat{\theta}_n, \theta_0) = O_p(n^{-\frac{r}{1+2r}})$.

Proof of Theorem 3

Denote V as the linear span of $\Theta_0 - \theta_0$, where θ_0 denotes the true value of $\theta = (\beta, \gamma, \varphi)$ and Θ_0 the true parameter space. Let $l(\theta, X)$ be the log-likelihood for a sample of size one and $\delta_n = (n^{-(1-\nu)/2} + n^{-r\nu})$. For any $\theta \in \{\theta \in \Theta_0 : d(\theta, \theta_0) = O(\delta_n)\}$, define the first order directional derivative of $l(\theta, X)$ at the direction $v \in V$ as

$$\dot{l}(\theta, X)[v] = \left. \frac{dl(\theta + sv, X)}{ds} \right|_{s=0},$$

and the second order directional derivative as

$$\ddot{l}(\theta, X)[v, \tilde{v}] = \left. \frac{d^2 l(\theta + sv + \tilde{s}\tilde{v}, X)}{d\tilde{s}ds} \right|_{s=0} \Big|_{\tilde{s}=0} = \left. \frac{d\dot{l}(\theta + \tilde{s}\tilde{v}, X)}{d\tilde{s}} \right|_{\tilde{s}=0}.$$

Define the Fisher inner product on the space V as $\langle v, \tilde{v} \rangle = P\{\dot{l}(\theta, X)[v]\dot{l}(\theta, X)[\tilde{v}]\}$ and the Fisher norm for $v \in V$ as $\|v\|^{1/2} = \langle v, v \rangle$. Let $\bar{V}$ be the closed linear span of V under the Fisher norm. Then $(\bar{V}, \|\cdot\|)$ is a Hilbert space. Also define the smooth functional of θ as $\gamma(\theta) = b'_1\beta + b'_2\gamma$, where $b = (b'_1, b'_2)'$ is any vector of $2p$ dimension with $\|b\| \leq 1$. For any $v \in V$, we denote

$$\dot{\gamma}(\theta_0)[v] = \left. \frac{d\gamma(\theta_0 + sv)}{ds} \right|_{s=0} = r(v),$$

whenever the right hand-side limit is well defined. Note that $\gamma(\theta) - \gamma(\theta_0) = \dot{\gamma}(\theta_0)[\theta - \theta_0]$. It follows by the Riesz representation theorem that there exists $v^* \in \bar{V}$ such that $\dot{\gamma}(\theta_0)[v] = \langle v^*, v \rangle$ for all $v \in \bar{V}$ and $\|v^*\|^2 = \|\dot{\gamma}(\theta_0)\|$.

Let ε_n be any positive sequence satisfying $\varepsilon_n = o(n^{-1/2})$. For any $v^* \in \Theta_0$, by (A4) and Corollary 6.21 of Schumaker (1981, p.277), there exists $\Pi_n v^* \in \Theta_n$ such that $\|\Pi_n v^* - v^*\| = o(1)$ and $\delta_n \|\Pi_n v^* - v^*\| = o(n^{-1/2})$. Also define $r[\theta - \theta_0, X] = l(\theta, X) - l(\theta_0, X) - \dot{l}(\theta, X)[\theta - \theta_0]$. Then

by definition of $\hat{\theta}$, we have

$$\begin{aligned}
0 &\leq P_n[l(\hat{\theta}, X) - l(\hat{\theta} \pm \varepsilon_n \Pi_n v^*, X)] \\
&= (P_n - P)[l(\hat{\theta}, X) - l(\hat{\theta} \pm \varepsilon_n \Pi_n v^*, X)] + P[l(\hat{\theta}, X) - l(\hat{\theta} \pm \varepsilon_n \Pi_n v^*, X)] \\
&= \pm \varepsilon_n P_n \dot{l}(\theta, X)[\Pi_n v^*] + (P_n - P) \left\{ r[\theta - \theta_0, X] - r[\hat{\theta} \pm \varepsilon_n \Pi_n v^* - \theta_0, X] \right\} \\
&\quad + P \left\{ r[\theta - \theta_0, X] - r[\hat{\theta} \pm \varepsilon_n \Pi_n v^* - \theta_0, X] \right\} \\
&= \mp \varepsilon_n P_n \dot{l}(\theta, X)[v^*] \pm \varepsilon_n P_n \dot{l}(\theta, X)[\Pi_n v^* - v^*] + (P_n - P) \left\{ r[\theta - \theta_0, X] \right. \\
&\quad \left. - r[\hat{\theta} \pm \varepsilon_n \Pi_n v^* - \theta_0, X] \right\} + P \left\{ r[\theta - \theta_0, X] - r[\hat{\theta} \pm \varepsilon_n \Pi_n v^* - \theta_0, X] \right\} \\
&:= \mp \varepsilon_n P_n \dot{l}(\theta, X)[v^*] + I_1 + I_2 + I_3.
\end{aligned}$$

For I_1 , with conditions (A1)-(A2), Chebyshev inequality and $\|\Pi_n v^* - v^*\| = o(1)$, we can conclude that $I_1 = o_p(n^{-1/2})\varepsilon_n$. For I_2 , we have

$$\begin{aligned}
I_2 &= (P_n - P) \left\{ l(\hat{\theta}, X) - l(\hat{\theta} \pm \varepsilon_n \Pi_n v^*, X) \pm \varepsilon_n \dot{l}(\theta_0, X)[\Pi_n v^*] \right\} \\
&= \mp \varepsilon_n (P_n - P) \left\{ \dot{l}(\tilde{\theta}, X)[\Pi_n v^*] - \dot{l}(\theta_0, X)[\Pi_n v^*] \right\},
\end{aligned}$$

310 where $\tilde{\theta}$ lies between $\hat{\theta}$ and $\hat{\theta} \pm \varepsilon_n \Pi_n v^*$. By Theorem 2.8.3 of van der Vaart and Wellner (1996), we know that $\{\dot{l}(\theta, X)[\Pi_n v^*] : \|\theta - \theta_0\| = O(\delta_n)\}$ is Donsker class. Therefore, by Theorem 2.11.23 of van der Vaart and Wellner (1996), we have $I_2 = \varepsilon_n \times o_p(n^{-1/2})$.

For I_3 , note that

$$\begin{aligned}
P(r[\theta - \theta_0, X]) &= P\{l(\theta, X) - l(\theta_0, X) - \dot{l}(\theta_0, X)[\theta - \theta_0]\} \\
&= 2^{-1} P\{\ddot{l}(\tilde{\theta}, X)[\theta - \theta_0, \theta - \theta_0] - \ddot{l}(\theta_0, X)[\theta - \theta_0, \theta - \theta_0]\} \\
&\quad + 2^{-1} P\{\ddot{l}(\theta_0, X)[\theta - \theta_0, \theta - \theta_0]\} \\
&= 2^{-1} P\{\ddot{l}(\theta_0, X)[\theta - \theta_0, \theta - \theta_0]\} + \varepsilon_n \times o_p(n^{-1/2}),
\end{aligned}$$

where $\tilde{\theta}$ lies between θ_0 and θ and the last equation is due to Taylor expansion, conditions (A1)-(A2) and $r > 2$. Therefore,

$$\begin{aligned}
I_3 &= -2^{-1} \{\|\hat{\theta} - \theta_0\|^2 - \|\hat{\theta} \pm \varepsilon_n \Pi_n v^* - \theta_0\|^2\} + \varepsilon_n \times o_p(n^{-1/2}) \\
&= \pm \varepsilon_n \langle \hat{\theta} - \theta_0, \Pi_n v^* \rangle + 2^{-1} \|\varepsilon_n \Pi_n v^*\|^2 + \varepsilon_n \times o_p(n^{-1/2}) \\
&= \pm \varepsilon_n \langle \hat{\theta} - \theta_0, v^* \rangle + 2^{-1} \|\varepsilon_n \Pi_n v^*\|^2 + \varepsilon_n \times o_p(n^{-1/2}) \\
&= \pm \varepsilon_n \langle \hat{\theta} - \theta_0, v^* \rangle + \varepsilon_n \times o_p(n^{-1/2}),
\end{aligned}$$

where the last equality holds because of Cauchy-Schwartz inequality and the facts that $\delta_n \|\Pi_n v^* - v^*\| = o(n^{-1/2})$ and $\|\Pi_n v^*\|^2 \rightarrow \|v^*\|^2$. Combing the above facts, together with $P\dot{l}(\theta_0, X)[v^*] = 0$, we can establish that

$$\begin{aligned} 0 &\leq P_n\{l(\hat{\theta}, X) - l(\hat{\theta} \pm \varepsilon_n \Pi_n v^*, X)\} \\ &= \mp \varepsilon_n P_n \dot{l}(\theta_0, X)[v^*] \pm \varepsilon_n \langle \hat{\theta} - \theta_0, v^* \rangle + \varepsilon_n \times o_p(n^{-1/2}) \\ &= \mp \varepsilon_n (P_n - P)\{\dot{l}(\theta_0, X)[v^*]\} \pm \varepsilon_n \langle \hat{\theta} - \theta_0, v^* \rangle + \varepsilon_n \times o_p(n^{-1/2}). \end{aligned}$$

Therefore, we obtain that $\sqrt{n} \langle \hat{\theta} - \theta_0, v^* \rangle = \sqrt{n}(P_n - P)\{\dot{l}(\theta_0, X)[v^*]\} + o_p(1) \rightarrow N(0, \|v^*\|^2)$, where the asymptotic normality is guaranteed by the central limits theorem and the asymptotic variance being equal to $\|v^*\|^2 = \|\dot{l}(\theta_0, X)[v^*]\|^2$. This together with condition (A5) implies that $n^{1/2}(\gamma(\hat{\theta}) - \gamma(\theta_0)) = n^{1/2} \langle \hat{\theta} - \theta_0, v^* \rangle + o_p(1) \rightarrow N(0, \|v^*\|^2)$ in distribution. The semiparametric efficiency can be established by applying the result of Bickel and Kwon (2001) or Theorem 4 in Shen (1997).

For each component ϑ_q , $q = 1, 2, \dots, 2p$, we denote by $\varphi_q^* = (b_{1q}^*, b_{2q}^*)$ the solution to

$$\inf_{\varphi_q^*} E \left\{ l_{\vartheta} \cdot e_q - l_{b_1^*} \cdot b_{1q}^* - l_{b_2^*} \cdot b_{2q}^* \right\}^2,$$

where $l_{\vartheta} = (l'_{\beta}, l'_{\gamma})'$, $l_{b_1^*}$ and $l_{b_2^*}$ are the partial derivatives of $l(\theta, X)$ with respect to b_1^* and b_2^* , respectively. Now let $\varphi^* = (\varphi_1^*, \dots, \varphi_q^*)$. By the calculations of Chen et al. (2006), we have

$$\|v^*\|^2 = \|\dot{\gamma}(\theta_0)\| = \sup_{v \in \mathbb{V}: \|v\| > 0} \frac{|\dot{\gamma}(\theta_0)[v]|}{\|v\|} = b' \Sigma b,$$

where $\Sigma = E(S_{\vartheta} S'_{\vartheta})$, $S_{\vartheta} = \{l_{\vartheta} - l_{b_1^*} b_1^* - l_{b_2^*} b_2^*\}$. Since $b'((\hat{\beta} - \beta_0)', (\hat{\gamma} - \gamma_0)') = \langle \hat{\theta} - \theta_0, v^* \rangle$, the conclusion of the theorem follows by the Cramér-Wold device.

References

- Betensky, R. A. and Finkelstein, D. M. (2002). Testing for dependence between failure time and visit compliance with interval-censored data. *Biometrics* **58**, 58–63.
- Bickel, P. J. and Kwon, J. (2001). Inference for semiparametric models: some questions and an answer. *Statist. Sinica* **11**, 863–960.
- Chen, X., Fan, Y., and Tsyrennikov, V. (2006). Efficient estimation of semiparametric multivariate copula models. *J. Amer. Statist. Assoc.* **101**, 1228–40.

- Chen, D.-G., Sun, J. and Peace, K. E. (2012). *Interval-Censored Time-to-Event Data: Methods and Applications*. Chapman & Hall/CRC.
- 330 Chen, Y.-H. (2010). Semiparametric marginal regression analysis for dependent competing risks under an assumed copula. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **72**, 235–51.
- Dennis Jr, J. E., and Schnabel, R. B. (1996). *Numerical methods for unconstrained optimization and nonlinear equations* (Vol. 16). Siam.
- Finkelstein, D. M. (1986). A proportional hazards model for interval-censored failure time data.
335 *Biometrics* **42**, 845–54.
- Finkelstein, D. M., Goggins, W. B. and Schoenfeld, D. A. (2002). Analysis of failure time data with dependent interval censoring. *Biometrics* **58**, 298–304.
- Goethals, K., Janssen, P. and Duchateau, L. (2008). Frailty models and copulas: similarities and differences. *Journal of Applied Statistics* **35**(9), 1071–9.
- 340 Goggins, W. B., Finkelstein, D. M., Schoenfeld, D. A. and Zaslavsky, A. M. (1998). A Markov chain Monte Carlo EM algorithm for analyzing interval censored data under the Cox proportional hazards model. *Biometrics* **54**, 1498–507.
- Hougaard, P. (2000). *Analysis of Multivariate Survival Data*. Springer, New York.
- Huang, J. (1996). Efficient estimation for the proportional hazards model with interval censoring.
345 *Ann. Statist.* **24**, 540–68
- Huang, J. and Rossini, A. J. (1997). Sieve estimation for the proportional odds failure- time regression model with interval censoring. *J. Amer. Statist. Assoc.* **92**, 960–67.
- Kalbfleisch, J. D., and Prentice, R. L. (2002). *The Statistical Analysis of Failure Time Data*, 2nd edn. Wiley, New York.
- 350 Lagakos, S. W. and Louis, T. A. (1988). Use of tumor lethality to interpret tumorigenicity experiments lacking cause-of-death data. *J. Appl. Stat.* **37**, 169–79.
- Lu, M., Zhang, Y., and Huang, J. (2007). Estimation of the mean function with panel count data using monotone polynomial splines. *Biometrika* **94**(3), 705–18.

- Nelsen, R. B. (2006). *An Introduction to Copulas* 2nd edn. Springer, New York.
- 355 Nosedal, J., and Wright, S. (2006). *Numerical Optimization*. Springer Science & Business Media.
- Pollard, D. (1984). *Convergence of Stochastic Processes*. Springer, New York.
- Ramsay, J. O. (1988). Monotone regression splines in action. *Statist. Sci.* **3**, 425–41.
- Schick, Q. and Yu, Q. (2000) Consistency of the GMLE with Mixed Case Interval-censored Data. *Scand. J. Statist.* **27**, 45–55.
- 360 Schumaker, L. L. (1981). *Spline Functions: Basic Theory* 3rd edn. Cambridge Mathematical Library.
- Shen, X. and Wong, W. H. (1994). Convergence rate of sieve estimates. *Ann. Statist.*, **22**, 580–615.
- Shen, X. (1997). On methods of sieves and penalization. *Ann. Statist.*, **25**, 2555–91.
- Sun, J. (2006). *The Statistical Analysis of Interval-Censored Failure Time Data*. Springer, New
 365 York.
- van de Geer, S. (2000). *Empirical Process in M-Estimation*. Cambridge University Press.
- van der Vaart, A. W. and Wellner, J. A. (1996). *Weak Convergence and Empirical Processes*. Springer, Berlin.
- Zhang, Y., Hua, L., and Huang, J. (2010). A spline-based semiparametric maximum likelihood
 370 estimation method for the Cox model with interval-censored data. *Scand. J. Stat.*, **37**, 338–54.
- Zhang, Z., Sun, L., Zhao X., and Sun, J. (2005). Regression analysis of interval-censored failure time data with linear transformation models. *Canad. J. Statist.*, **33**, 61–70.
- Zhang, Z., Sun, L., Sun, J. and Finkelstein, D. M. (2007). Regression analysis of failure time data with informative interval censoring. *Stat. Med.* **26**, 2533–46.
- 375 Zheng, M., Klein, J. P. (1995). Estimates of marginal survival for dependent competing risk based on an assumed copula. *Biometrika*, **82**, 127–138.